TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

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Abstract

A method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells is disclosed. The method comprises the administration of a compound of formula (1.0) to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human being. Novel compounds of formulae (5.0, 5.1, 5.2, 5.3, 5.3A and 5.3B) are disclosed. Also disclosed are processes for making 3-substituted compounds of formulae (5.0, 5.1, 5.2 and 5.3). Further disclosed are novel compounds which are intermediates in the process for making 3-substituted compounds of formulae (5.0, 5.1, 5.2 and 5.3).

Description

TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

BACKGROUND

International Publication Number W092/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:

wherein the dotted line represents an optional double bond, Xis hydrogen or haio, and Y is hydrogen, substituted carboxylate or substituted sulfonyl. For example, Y can be, amongst others, -COOn wherein R is C1 to C6 alkyl or substituted alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl or -2, -3, or -4 piperidyl or
N-substituted piperidyl. Y can also be, amongst others, SO2R wherein R is C1 to C6 alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl. Examples of such potentiating agents include 11-(4 piperidylidene)-5 H-benzo[5 ,6]cyclohepta[1 ,2-b]pyridines such as
Loratadine.

Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth indesendent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by
Formula 1.0:

or a pharmaceutically acceptable salt or solvate thereof, wherein:
one of a, b, c and d represents N or NR9 wherein R9 is O', -CH3 or -(CH2)nCO2H wherein n is 1 to 3, and

the remaining a, b, c and d groups represent CR1 or CR2; or
each of a, b, c, and d are independently selected from CR1 or CR2;
each R1 and each R2 is independently selected from H, halo, -CF3, -OR10 (e.g., -OCH3), -COR10, -SR10 (e.g., -SCH3 and -SCH2C6H5), -S(O)tR11 (wherein t is 0,1 or 2, e.g., -SOCH3 and -SO2CH3), -N(R10)2, -NO2, -OC(O)R10, -C02R10, -OC02R11 -CN, -NR10COOR11, -SR11C(O)OR11 (e.g., -SCH2CO2CH3), -SR11N(R75)2 wherein each R75 is independently selected from H and -C(O)OR11 (e.g., -S(CH2)2NHC(O)O-t-butyl and -S(CH2)2NH2), benzotriazol-l -yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1 -methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR10 or -C02R10;
R3 and R4 are the same or different and each independently represents H, any of the substituents of R1 and R2, or R3 and R4 taken together represent a saturated or unsaturated C5.C7 fused ring to the benzene ring (Ring III);
R5, R6, R7 and R8 each independently represents H, -CF3, -COR10, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR10.

-SR10, -S(O)tR11, -NR1 0COOR1 1, -N(R10)2, -NO2, -COR10, -OCOR10, -OCO2R, -C02R10, OP03R10 or one of R5, R6, R7 and R8 can be taken in combination with R40 as defined below to represent -(CH2)r wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, -CF3 or aryl, or R5 is combined with R6 to represent =0 or =S and/or R7 is combined with R8 to represent =0 or =S;
R10 represents H, alkyl, aryl, or aralkyl (e.g., benzyl);
R11 represents alkyl or aryl;
X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11; ;
the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -R10, halo, -OR, -OCO2R1 1 or -OC(O)R10, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H2, -(OR11)2; H and halo, dihalo, alkyl and
H, (alkyl)2, -H and -OC(O)R10, H and -OR10, =0, aryl and H, =NOR10 or -O-(CH2)p-O- wherein p is 2, 3 or 4;
R represents R40, R42, R44, or R54, as defined below;
R40 represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents

wherein R3 and R4 are as previously defined and W is O, S or NR10 wherein R10 is as defined above; said R40 cycloalkyl, alkenyl and alkynyl
groups being optionally substituted with from 1-3 groups selected from halo, -CON(R10)2, aryl, -CO2R10, -OR, -SR, -N(R10)2, -N(R10)C02R11, -COR12, -NO2 or D, wherein -D, R10 and R11 are as defined above and R12 represents R10, -(CH2)mOR1o or -(CH2)qC02R10 wherein R10 is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R40 groups not containing -OH, -SH or -N(R10)2 on a carbon containing a double or triple bond respectively; or
R40 represents phenyl substituted with a group selected from -SO2NH2, -NHSO2CH3, -SO2NHCH3, -SO2CH3, -SOCH3, -SCH3, or -NHSO2CF3, preferably, said group is located in the para (p-) position of the phenyl ring; or
R40 represents a group selected from

R42 represents

wherein R20, R21 and R46 are each independently selected from the group consisting of:
(1) H;
(2) -(CH2)qSC(O)CH3 wherein q is 1 to 3 (e.g., -CH2SC(O)CH3);
(3) -(CH2)qOSO2CH3 wherein q is 1 to 3 (e.g., -CH2OSO2CH3);
(4) -OH;
(5) -CS(CH2)w(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl (e.g., -C-$-CH2-4-methoxyphenyl);
(6) -NH2;
(7) -NHCBZ (wherein CBZ stands for carbonylbenzyloxy--i.e.,
CBZ represents -C(O)OCH2C6H5); ;
(8) -NHC(O)OR22 wherein R22 is an alkyl group having from 1 to 5 carbon atoms (e.g., R22 is t-butyl thus forming -NHBOC wherein BOC stands for tert-butyloxycarbonyl--i.e., BOC represents -C(O)OC(CH3)3), or

R22 represents phenyl substituted with 1 to 3 alkyl groups (e.g., 4methylphenyl);
(9) alkyl (e.g., ethyl);
(10) -(CH2)kphenyl wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);
(11) phenyl;
(12) substituted phenyl (i.e., phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from the group consisting of: halo (e.g., Br, Cl, or I, with Br being preferred); NO2; -OH; -OCH3; -N H2; -NHR22; -N(R22)2; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred); -O(CH2)tphenyl (wherein t is from 1 to 3 with 1 being preferred); and -O(CH2) tsubstituted phenyl (wherein t is from 1 to 3 with 1 being preferred); examples of substituted phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, onitrophenyl, m-hydroxy-phenyl, o-hydroxyphenyl, methoxyphenyl, pmethylphenyl, m-methyl-phenyl, and -OCH2C6H5;
(13) naphthyl;
(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;
(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (e.g., adamantyl and norbornyl);
(16) cycloalkyl having from 5 to 7 carbon atoms (e.g., cyclopentyl, and cyclohexyl);
(17) heteroaryl (e.g., pyridyl, and pyridyl N-oxide);
(18) hydroxyalkyl (e.g., -(CH2)VOH wherein v is 1 to 3, such as, for example, -CH2OH); ;
(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacernent of the hydrogen bound to said carbon;

(23) -NHC(O)-(CH2)k-phenyl or -NH(O)-(CH2)k-substitued phenyl, wherein said k is as defined above (i.e., 1-6, usually 1-4 and preferably 1);
(24) piperidine Ring V:

wherein R50 represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., CH3C(O)-), alkyloxycarbonyl (e.g., -C(O)O-t-C4Hg, -C(O)OC2H5, and -C(O)OCH3), haloalkyl (e.g., trifluromethyl), or --C(O)NH(R10) wherein
R10 is H or alkyl; Ring V includes

examples of Ring V include:

(25) -NHC(O)CH2C6H5 or -NHC(O)CH2-substituted-C6H5, for example -NHC(O)CH2-p-hydroxyphenyl, -NHC(O)CH2-m-hydroxyphenyl, and -NHC(O)CH2-o-hydroxyphenyl;
(26) -NHC(O)OC6HD;

(30) -OC(O)-heteroaryl, for example

(31) -O-alkyl (e.g., -OCH3); and
(32) -CF3; or
R20 and R21 taken together form a =0 group and the remaining
R46 is as defined above; or
Two of R20, R21 and R46 taken together form piperidine Ring V

wherein R50 represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., CH3C(O)-), alkyloxycarbonyl (e.g., -C(O)O-t-C4Hg, -C(O)OC2H5, and -C(O)OCH3), haloalkyl (e.g., trifluro-methyl), or -C(O)NH(R10) wherein
R10 is H or alkyl; Ring V includes

examples of Ring V include:

with the proviso that R46, R20, and R21 are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e., R46, R20, and R21 are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);
R44 represents

wherein R25 represents heteroaryl (e.g., pyridyl or pyridyl N-oxide) or aryl (e.g., phenyl and substituted phenyl); and R48 represents H or alkyl (e.g., methyl);
R54 represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):

wherein R56, R58, and R60 are the same or different and each is independently selected from H, halo, -CF3, -OR10, -C(O)R10, -SR10, -S(O)eR11 (wherein e is 1 or 2), -N(R1)2, -NO2, -C02R10, -OC02R11, -OCOR10, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with -OR10, -SR10 or -N(R10)2 and which alkenyl may be substituted with
OR11 or SR11; or
R54 represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):

wherein Y represents N+-O- and E represents N; or
R54 represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia) (iiia) or (iva);
Z represents 0 or S such that R can be taken in combination with
R5, R6, R7 or R8 as defined above1 or R represents R40, R42, R44 or R54.

Examples of R20, R21, and R46 for the above formulas include:

Examples of R25 groups include:

wherein Y represents N or NO, R28 is selected from the group consisting of: C1 to C4 alkyl, halo, hydroxy, NO2, amino (-N H2), -NHR30, and -N(R30)2 wherein R30 represents C1 to C6 alkyl.

Tricyclic compounds useful in the methods of this invention are described in: (1) U.S. 5,151,423; (2) U.S. 4,826,853; (3) U.S. 5,089,496; (4) WO 88/03138 published on May 5, 1988 (PCT/US87/02777); and (5) U.S. 5,104,876; the disclosures of each being incorporated herein by reference thereto. Those compounds within the scope of this invention which are not described in these documents are described herein.

This invention also provides novel compounds of Formula 1.0 having the formula:

wherein all substituents are as defined for Formula 1.0
This invention further provides novel compounds of Formula 1.0 having the formula:

wherein all substituents are as defined for Formula 1.0
Additionally, this invention provides novel compounds of Formula 1.0 having the formula:

wherein all substituents are as defined for Formula 1.0.

Compounds of Formula 5.2 include compounds wherein the substituents R20, R21, and R46 are selected such that when one of said substituents R20, R21, and R46 (e.g., R46) is selected from the group consisting of: (1) H, (2)-OH, (3)-NH2, (4) -NHC(O)OR22, (5) alkyl, (6) phenyl, (7) heteroaryl, (8) hydroxyalkyl, (9) substituted pyridyl, (10) substituted phenyl and (11) -O-alkyl, then the remaining two of said substituents R20, R21 and R46 (e.g., R20 and R21) cannot both be H when: (a) R1 and R2 are both H, and (b) the double bond between C-5 and C-6 is absent, and (c) both A and B are H2, and (d) R4 is H, and (e) R3 is H or
Cl at C-8. Compounds of Formula 5.2 also include compounds wherein when R46 is a group (1) to (11) defined above then R20 and R21 cannot both be H when: R1 and R2 are both H, and both A and B are H or H2.

Compounds of Formula 5.2 further include compounds wherein when R46 is a group (1) to (11) defined above then R20 and R21 cannot both be H when R1 and R2 are both H. Compounds of Formula 5.2 also include compounds wherein two of R20, R21 and R46 are not H when R1 and R2 are both H.

This invention further provides novel compounds of Formula 1.0 having the formula:

wherein all the substituents are as defined for Formula 1.0. Preferably
R25 represents heteroaryl.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment.

In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myeiodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

This invention also provides a process for producing 3-nitro substituted compounds. The process comprises reacting one molar equivalent of a compound:

wherein Ri, R2, R3, R4, A, B, a, b, d, and the dotted lines are as defined for
Formula 1.0; and R65 represents H or -OR66 wherein R66 represents alkyl (e.g., C1 to C4 alkyl, preferably ethyl); with one molar equivalent of a nitrating reagent, said nitrating reagent being preformed (i.e., prepared first) by mixing, at cold temperature (e.g., at OOC) equimolar amounts of tetrabutyl ammonium nitrate with trifluoroacetic anhydride; the reaction of the nitrating reagent with the compound of Formula 1.0g taking place in a suitable aprotic solvent (e.g., methylene chloride, chloroform, toluene or tetrahydrofuran); said reaction with said nitrating reagent being conducted at a temperature and for a period of time sufficient to allow the reaction to proceed at a reasonable rate to produce the desired final 3-nitro compound of Formula 1.0h (described below)--i.e., the reaction of the compound of Formula 1 .0g with said nitrating reagent is conducted at an intial temperature of 0 C, and said reaction temperature is thereafter allowed to rise to about 250C during the reaction time period. The reaction usually proceeds overnight to completion, i.e., the reaction usually proceeds for about 16 hours. The reaction can be conducted within a temperature of 0 C to about 25"C during a time period of about 10 to about 24 hours. Preferably the reaction is initially conducted at 0 C and the temperature is allowed to warm up to 250C. The reaction produces the 3-nitro compound:

The compound of Formula 1.0h can then be converted to other 3substituted products by methods well known to those skilled in the art. For example, the 3-nitro compounds can be converted to 3-amino, 3-halo, 3cyano, 3-alkyl, 3-aryl, 3-thio, 3-arylalkyl, 3-hydroxyl, and 3-OR67 wherein
R67 is alkyl or aryl. The 3-substituted compounds can then be converted to final products (wherein R65 is R42 or R44) by the procedures described herein.

This invention also provides a process for producing 3-nitro compounds of the formula:

by producing a compound of Formula 1.0h from 1 .0g as described above; and then hydrolyzing the compound of Formula 1.0h by dissolving the compound of Formula 1.0h in a sufficient amount of concentrated acid (e.g., concentrated HCl or aqueous sulfuric acid), and heating the resulting mixture to a temperature sufficient to remove (hydrolyze) the -C(O)R65 substituent, for example, heating to reflux or to a temperature of about 100 C. This hydrolysis process is exemplified in Preparative
Example 28.

The compound of Formula 1.0i can then be converted to other 3substituted compounds as discussed above for the compounds of
Formula 1.0h. The compounds of Formula 1.0i can then be converted to compounds of this invention by the methods described herein.

This invention also provides a process for producing compounds of the formula:

by reacting one molar equivalent a compound of formula:

with one molar equivalent of a nitrating reagent, said nitrating reagent being preformed (i.e., prepared first) by mixing, at cold temperature (e.g., at 0 C) equimolar amounts of tetrabutyl ammonium nitrate with trifluoroacetic anhydride; the reaction of the nitrating reagent with the compound of Formula 1.0k taking place in a suitable aprotic solvent (e.g., methylene chloride, chloroform, toluene or tetrahydrofuran); said reaction with said nitrating reagent being conducted at a temperature and for a period of time sufficient to allow the reaction to proceed at a reasonable rate to produce the desired final 3-nitro compound of Formula 1.0j--i.e., the reaction of the compound of Formula 1.0k with said nitrating reagent is conducted at an intial temperature of 0 C, and said reaction temperature is thereafter allowed to rise to about 250C during the reaction.time period.

The reaction usually proceeds overnight to completion, i.e., the reaction usually proceeds for about 16 hours. The reaction can be conducted within a temperature of 0 C to about 25"C during a time period of about 10 to about 24 hours. Preferably the reaction is initially conducted at OOC and the temperature is allowed to warm up to 250C. In Formulas 1.0j and 1.0k, R1, R2, R3, R4, A, B, a, b, d, and the dotted lines are as defined for
Formula 1.0
The compounds of Formula 1.0j can be converted to compounds of
Formula 1.0h by methods described below. Also, as discussed above for the compounds of Formula 1.0h, the compounds of Formula 1.0j can be converted to other 3-substituted compounds wherein the substituents are those discussed above for Formula 1.0h.

The compounds of Formula 1.0j can be converted to compounds of
Formula 1.0m:

wherein R68 is H or -COORa wherein Ra is a C1 to C3 alkyl group (preferably R68 is H), by reducing a compound of Formula 1.0j with a suitable reducing agent (such as sodium borohydride) in a suitable solvent (such as ethanol or methanol) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., 0 to about 250C); reacting the resulting product (Formula 1.0j wherein the =0 has been reduced to a -OH) with a chlorinating agent (e.g., thionyl chloride) in an suitable organic solvent (e.g., benzene, toluene or pyridine) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., about -20 to about 200C, preferably at -1 50C, see, for example Preparative Example 7) to produce a compound of Formula 1.0n:

and reacting a compound of Formula 1.0n with a compound of the formula: :

wherein R68 is as previously defined, and is preferably H, in a suitable organic solvent (such as tetrahydrofuran or toluene) containing a suitable base (such as triethylamine or N-methylmorpholine) at a suitable temperature to allow the reaction to proceed at a reasonable rate (e.g., 25 to about 1200C).

Compounds of Formula 1.0m can be converted to compounds of this invention by the methods disclosed herein. Also, as discussed above for the compounds of Formula 1.0h, the compounds of Formula 1.0m can be converted to other 3-substituted compounds wherein the substituents are those discussed above for Formula 1.0h.

This invention also provides novel compounds (produced in the above described processes as intermediates to the compounds of this invention) having the formulas:

wherein all substituents are as defined herein.

Preferably, for the intermediate compounds of the processes of this invention, R1 and R2 are H; R3 is halo, most preferably Cl, in the C-8 position; R4 is H; and A and B are H when the double between C-5 and C6 is present, and A and B are H2 when the bond between C-5 and C-6 is a single bond (most preferably the bond between C-5 and C-6 is a single bond). Those skilled in the art will appreciate that Rings I, II, and/or III can be further substituted, as described herein, to produce the desired compounds of the invention.

Examples of such novel intermediate compounds include:

DETAILED DESCRIPTION OF THE INVENTION
As used herein, the following terms are used as defined below unless otherwise indicated:
M+-represents the molecular ion of the molecule in the mass spectrum;
MH+-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;
Bu-represents butyl;
Et-represents ethyl;
Me-represents methyl;
Ph-represents phenyl;
benzotriazol-1-yloxy represents

1-methyl-tetrazol-5-ylthio represents

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms; ;
alkanediyl-represents a divalent, straight or branched hydrocarbon chain having from 1 to 20 carbon atoms, preferably 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene, -CH2CH2CH2-, -CH2CHCH3, -CHCH2CH3, etc.

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;
heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -0--S- or - NR10-(suitable heterocycloalkyl groups including 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, etc.);
alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms; ;
alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;
aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF3, amino, alkylamino, dialkylamino, -COOR10 or -NO2; and
halo-represents fluoro, chloro, bromo and iodo; and
heteroaryl-represents cyclic groups, optionally substituted with R3 and R4, having at least one heteroatom selected from 0, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R3 and R4),wherein pyridyl N-oxide can be represented as:

Reference to the position of the substituents R1, R2, R3, and R4 is based on the numbered ring structure:

For example, R1 can be at the C-4 position and R2 can be at the C-2 or
C-3 position. Also, for example, R3 can be at the C-8 position and R4 can be at the C-9 position.

Representative structures of Formula 1.0 include but are not limited to:

Preferably, for the compounds of Formula 1.0 (including 1.0a to 1.0d):
each of a, b, c, and d are C (carbon); or
one of a, b, c and d (most preferably a) represents N or NO, most preferably N, and the remaining a, b, c and d groups represent CR1 or
CR2;
each R1 and each R2 is independently selected from H, halo (e.g.,
Cl, Br and F), -CF3, -OR10 (e.g., hydroxy and alkoxy (e.g., -OCH3)), alkyl (e.g., methyl and t-butyl, said alkyl group being optionally substituted with halo), benzotriazol-1 -yloxy, -S(O)tR11 (e.g., -SCH2CH3), -SR11 C(O)OR (e.g., -SCH2CO2CH3), -SR10 (e.g., R10 represents -CH2C6H5) and 1methyl-tetrazol-5-ylthio; most preferably Rt and R2 are independently H, halo, -CF3, lower alkyl (e.g., C1 to C4, more preferably methyl) or benzotriazol-1-yloxy; more preferably R1 is Cl or H, and R2 is H, Cl or Br; still more preferably R1 is at the C-4 position, and R2 is at the C-3 position; even more preferably R2 is Br or H;
R3 and R4 are the same or different and each independently represents H, halo, -CF3, -OR10, -COR10, .SR1O, -S(O)tR11 (wherein t is 0, 1 or 2), -N(R10)2, -NO2, -OC(O)R10, -CO2R10, -OCO2R11, -CN, -NR10COOR11, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR10 or -CO2R10; most preferably
R3 and R4 independently represent H, halo, -CF3, -OR10 or alkyl (said alkyl group being optionally substituted with halo); more preferably R3 and R4 independently represent H or halo (e.g., Cl, Br, or F); even more
preferably R3 is at the C-8 position and R4 is at the C-9 positon; still more
preferably R3 is Cl at theC-8 position and R4 is H at the C-9 position;
R5, R6, R7 and R8 each independently represents H, -CF3 or alkyl
(said alkyl optionally being substituted with -OR10); most preferably R5,
R6, R7 and R8 independently represent H and alkyl, and more preferably
H;
when the optional double bond between carbon atoms 5 and 6 is present, A and B independently represent H, -R10 or -OR10, most preferably H, lower alkyl (C1 to C4) and alkyloxy (i.e., Rio represents alkyl), more preferably H and -OH, and still more preferably H; and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H2, -(OR10)2, alkyl and H, (alkyl)2, - H and -OR10 or =0, most preferably H2, -H and -OH, or =0, and more preferably A represents H2 and B represents H2 or =O;
R represents R42 or R44; and
Z represents 0 or S, and most preferably 0.

Compounds of Formula 5.0 include:

Compounds of Formula 5.1 include:

Compounds of Formula 5.2 additionally include:

Compounds of Formula 5.3 include:

Compounds of formula 5.3A include:

For the compounds of Formulas 5.0, 5.0a-5.0g, 5.1, 5.1a-5.1g, 5.2, 5.2a-5.2b, 5.3, 5.3a-5.3g, 5.3A, 5.3Aa-5.3Ag, and 5.3B, the definitions of the substituents are as defined for Formula 1.0.

Preferably, for compounds of Formulas 5.0, 5.0a-5.0g, 5.1, 5.1 an 5.lg, 5.2, and 5.2a-5.2b, R46 is selected from piperidine Ring V, heteroaryl, phenyl, substituted phenyl, substitued pyridyl or substituted pyridyl N-oxide, and R20 and R21 are independently selected from H or alkyl. Most preferably, R46 is pyridyl, pyridyl N-oxide or piperidine Ring V.

More preferably, R46 is pyridyl, pyridyl N-oxide or piperidine Ring V and both R20 and R21 are hydrogen or both R20 and R21 are alkyl (still more preferably methyl).

Even more preferably, R46 is selected from 3-pyridyl, 4-pyridyl, 3pyridyl N-oxide, 4-pyridyl N-oxide, 4-N-methylpiperidinyl, 3-Nmethylpiperidinyl, 4-N-acetylpiperidinyl or 3-N-acetylpiperidinyl, and both R20 and R21 are hydrogen or both R20 and R21 are alkyl (still even more preferably methyl). Even still more preferably, R46 is selected from 3pyridyl, 3-pyridyl N-oxide, 4-pyridyl, and 4-pyridyl N-oxide, and both R20 and R21 are hydrogen or both R20 and R21 are methyl.

Examples of the R42 groups include:

Preferably for the compounds of Formulas 5.3, 5.3a-5.3g, 5.3A, 5.3Aa-5.3Ag, and 5.3B, R25 represents phenyl, 2-pyridyl, 3-pyridyl or 4pyridyl, and most preferably 3-pyridyl. More prefereably, R48 represents H or methyl and still more preferably H.

Representative compounds of the invention include:

Preferred compounds of this invention are selected from the group consisting of compounds of Examples: 1, 2, 3, 4, 5, 6, 19, 42, 43, 44, 45, 46, 47, 48, 49, 75, 76, 78, 82, 83, 84, 85, 89, 121, 180, 182, 183, 184,187 (6.7 and 6.8), 192, 196, 197, 198, 200, 201, 206, 222, 223, 224, 225, 226, 227, 233, 234, 236, 239, 246, 247, 248, 249, 250, 251, 261, 262, 266, 267, 269, 273, 276, 283, 285, 286, 287, 288, 289, 291, 292, 293, 299, 300, 301, 303, 307, 309, 311, 312, 313, 314, 316, 350, 351, 352,354 and 356.

More preferred compounds of this invention are selected from the group consisting of compounds of

Examples: 1, 2, 42, 43, 75, 78, 82, 180, 183, 187 (6.7 and 6.8), 196, 197, 198, 200, 222, 223, 224, 227, 233, 234, 246, 247, 248, 249, 250, 251, 266, 269, 273, 283, 285, 286, 291, 292, 300,301,303,307,311, 312, 313, 314, 350, 351, 352,354 and 356.

Even more preferred compounds of this invention are selected from the group consisting of compounds of Examples: 82, 197, 233, 246, 266, 312, 351, 352, 354 and 356.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines,
N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyridonitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula 1.0 wherein R is -N(R10)2, and compounds of Formulas 5.3, 5.3A and S.3B can be prepared by reacting compound 405.00 (described below) with an isocyanate (R10-N=C=O) in a solvent such as DMF, dichloromethane or THF in accordance with methods known in the art.

The following processes may be employed to produce compounds of the invention--i.e., compounds of Formula 1.0 represented by compounds of Formulas 5.0, 5.1, 5.2 and 5.3. For purposes of describing the processes, the compounds are represented by Formula 400.00:

wherein R represents R42 or R44, and all other substitutents are as described herein.

A. A compound of Formula 405.00 may be coupled with a compound of the formula RCOOH in the presence of coupling agent such as 1 -(3-dimethylam inopropyl)-3-ethyl carbodiimde hydrochloride (DEC), N,N'-dicyclohexylcarbodiimide (DCC) or N,N'-carbonyl-diimidazole (CDI) to produce compounds of Formula 400.00:

The reaction is usually conducted in an inert solvent such as tetrahydrofuran, DMF or methylene chloride at a temperature between about OOC and reflux, preferably at about room temperature. When the coupling agent is DCC or DEC, the reaction is preferably run in the presence of 1-hydroxybenzotriazole (HOBT). Method A is the method of choice for preparing compounds of this invention.

B. A compound of Formula 405.00 may also be reacted with a compound of Formula 410.00 in the presence of base to produce compounds of Formula 400.00:

405.00 + RC(O)L > 400.00.

(410.00)

Representative examples of appropriate bases are pyridine and triethylamine. L designates a suitable leaving group. For example, a compound of compound 410.00 may be an acyl halide (e.g., L represents halo) or an acyl anhydride, (e.g., L is -O-C(O)-R). The leaving group may also be alkoxy, in which case the compounds of Formula 400.00 may be produced by refluxing a compound of Formula 405.00 with an excess of a compound of Formula 410.00.

Compounds of Formula 405.00 may be prepared by cleaving the group COORa from the corresponding carbamates 415.00, for example, via acid hydrolysis (e.g., HCl) or base hydrolysis (e.g., KOH):

wherein Ra is a group which does not prevent the cleavage reaction, e.g.,
Ra is an optionally substituted alkyl such as ethyl.

Alternatively, depending upon the nature of Ra, as determined by one skilled in the art, Compound 415.00 may be treated with an organometallic reagent (e.g., CH3Li), a reductive reagent (e.g., Zn in acid), etc., to form compounds of Formula 405.00.

Compound 415.00 may be prepared from the N-alkyl compound shown as Formula 420.00 below, in the manner disclosed in U.S. Patents 4,282,233 and 4,335,036.

A B
\= 5 n3
4
ba
x t 415.00
3r, R7
Na
(420.00) alkyl

It also will be apparent to one skilled in the art that there are other methods for converting Compound 420.00 to Compound 405.00. For example, treatment of Compound 420.00 with BrCN via von Braun reaction conditions would provide nitrile 420.00a. Subsequent hydrolysis of the nitrile under either aqueous basic or acidic conditions would produce Compound 405.00. This method is preferable when there is substitution on the piperidine or piperazine ring.

A B
R1
C
t
R5,,
R6 p8
(420.00) 1 B
alkyl "xd A
Ri R3
R2 < 3R4
ba 11
'RB
(420.00a) I
CN

<#s> C. The compounds of Formula 400.00 wherein Z is O or S may
be made by an alternative process using direct conversion of the N-alkyl compound 420.00 with an appropriate compound of Formula 410.00 such as an acyl halide or acyl an hydride. Preferably the reaction is run in the presence of an appropriate nucleophile (e.g. LiI, etc.) and solvent (e.g., toluene, dioxane or xylenes). An appropriate base, may be added, and heating may be required. Typically, a temperature ranging from 50-150"C (preferably 100-120"C) is utilized.

n1 dA{gjB R3
A B
W
R2 Z
a' 11 II
R-C-L
base 40000
~ Xs > 400.00
R5 > R7 heat
R6H R8
N
(420.00)
alkyl

Compound 420.00 is prepared as described in part B above.

PREPARATION OF SINGLE BOND COMPOUNDS
Compounds of Formula 400.00, wherein X is carbon and the bond to carbon 11 (Cell) is a single bond, can be prepared by reducing compounds of Formula 405.00, wherein X is carbon and the bond to C-I I is a double bond, with lithium aluminum hydride in tetrahydrofuran.

Conversion to final products can be done following the process described above for conversion of compounds of Formula 405.00 to compounds of
Formula 400.00.

PREPARATION OF DOUBLE BOND COMPOUNDS
Compounds of Formula 400.00, wherein X is a carbon atom having an exocyclic double bond to carbon 11, may be prepared from compound 420.00 as described above. Compounds of Formula 420.00 may be produced by the methods disclosed generally in U.S. Patent 3,326,924 or alternatively may be prepared by a ring closure reaction, wherein the desired cycloheptene ring is formed by treating compound 425.00 with a super acid. Suitable super acids for this purpose include, for example,
HF/BF3, CF3SO3H (triflic acid), CH3SO3H/BF3, etc. The reaction can be performed in the absence of, or with, an inert co-solvent such as CH2C12.

The temperature and time of the reaction vary with the acid employed. For example, with HF/BF3 as the super acid system the temperature may be controlled so as to minimize side reactions, such as HF addition to the exocyclic double bond. For this purpose, the temperature is generally in the range of from about +50C to -50 C. With CF3SO3H as the super acid system, the reaction may be run at elevated temperatures, e.g., from about 250C to about 1500C and at lower temperatures but the reaction then takes longer to complete.

Generally the super acid is employed in excess, preferably in amounts of from about 1.5 to about 30 equivalents.

A B
,
R2 R5
R5 R7
R6----R8 acid
N
(425.00) alkyl A B
alkyl
R2 9 4
ba
R5 7
R ç > R8
RYE FIX
(420.00)
alkyl

A ketone compound of Formula 425.00 may be formed by hydrolysis of 430.00, e.g., such as by reacting a Grignard intermediate of
Formula 430.00 with an aqueous acid (e.g., aqueous HCI). Ia in Formula 430.00 represents chloro, bromo or iodo.

A B
R1d R3
c I
R2
R2 - ----------t 425.00
R6,, 'R89Ra7
R7
R6 R8
N
(430.00) alkyl

The Grignard intermediate 430.00 is formed by the reaction of the cyano compound 435.00 with an appropriate Grignard reagent 440.00 prepared from 1-alkyl-4halopiperidine. The reaction is generally performed in an inert solvent, such as ether, toluene, or tetrahydrofuran, under general Grignard conditions e.g., temperature of from about 0 C to about 75"C. Alternatively, other organometallic derivatives of the 1alkyl-4halo piperidine can be employed.

A B M gla
R' R5 R7
+
R2 > I Re$; R8
CN N
(440.00)
(435.00) alkyl
430.00

The cyano compound of Formula 435.00 is produced by converting the tertiary butyl amide of Formula 445.00 with a suitable dehydrating agent, such as POCI3, SOCh, P205, toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with a co-solvent, such as xylene.

The dehydrating agent such as POCI3 is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for

performing the reaction, but generally heat is added to accelerate the reaction. Preferably the reaction is performed at or near reflux.

The tert-butylamide of Formula 445.00 may be produced by reaction of a compound of Formula 450.00a and 450.00b, in the presence of base, wherein G is chloro, bromo or iodo.

The compound of Formula 450.00a may be formed by hydrolysis of the corresponding nitrile wherein the appropriate cyanomethyl pyridine, such as 2-cyano-3-pyridine, is reacted with a tertiary butyl compound in acid, such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid. Suitable tertiary butyl compounds include, but are not limited to, t-butyl alcohol, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending upon the reactants, but generally the reaction is conducted in the range of from about 500C to about 1 000C with t-butyl alcohol. The reaction may be performed with inert solvents, but is usually run neat.

An alternative process for the formation of compounds of Formula 400.00a may involve direct cyclization of Compound 455.00 as shown below.

Cyclization to form the cycloheptene ring may be accomplished with a strong acid (e.g., triflic, polyphosphoric, HF/BF3), and may be performed in an inert solvent, such as ether, toluene or THF. The temperature and time may vary with the acid employed, as described in process A above.

Compounds of Formula 455.00 wherein Z = O or S may be prepared by treating a compound of Formula 425.00 with an appropriate acyl halide or acyl anhydride of formula 410.00. Most preferably this reaction is run in the presence of a good nucleophile, such as Lii, in the appropriate solvent, such as toluene, dioxane or xylene, and at a temperature ranging from 50-150"C, preferably 100-1 200C.

410.000
425.00 + # 455.00

A second method of preparing compounds of Formula 455.00 involves reacting an unsubstituted piperidylidene compound of Formula 460.00 with the appropriate acyl halide or acyl anhydride of Formula 410.00 in the presence of base, such as pyridine or triethylamine.

Alternatively, if L = OH in compound 410.00 then coupling of compound 460.00 with compound 410.00 may require use of a conventional coupling reagent, such as DCC or CDI.

Compounds of Formula 460.00 may be produced from the
corresponding carbamates of Formula 465.00, via acid hydrolysis, using
for example, aqueous hydrochloric acid, or base hydrolysis using for example, potassium hydroxide. Alternatively, some compounds can be prepared by treating the carbamate, Formula 465.00, with an organometallic reagent, such as methyl lithium or a reductive reagent, such as zinc in acid, etc., depending upon the nature of the Ra group. For example, if Ra is a simple alkyl group, Copra may be cleaved by alkaline hydrolysis at 1000C.

The carbamate compounds of Formula 465.00 may be prepared from the appropriate alkyl compound of Formula 425.00 by treatment with a chloroform ate, preferably in an inert solvent, such as toluene, with warming to approximately 80"C. Other alternative methods are available for the conversion of 425.00 to

455.00 as previously described (e.g. Von
Braun reaction conditions). Compounds of Formula 425.00 may be prepared as described above.

SUBSTITUTION ON THE PYRIDINE RING
Various methods can be used as described in WO 88/03138 to provide compounds which are substituted on the pyridine ring, i.e., in positions 2-, 3- and or 4- positions of the tricyclic ring system. For example, the cyclization methods described on pages 20-30 of WO 88/03138 can already have the appropriate substituents on the pyridine ring in place. A variety of substituted pyridines are known in the literature and can be employed in these syntheses. Alternatively, the azaketone of
Formula XIX (from page 27 of WO 88/03138)

wherein R1 and R2 are both H can be converted to the appropriately substituted azaketone wherein R1 and R2 are non-H substitutents. If both R1 and R2 are desired to be non-H substitutents the procedure would be repeated.

The azaketone is thus reacted with an oxidizing agent such as meta-chloroperoxybenzoic acid (MCPBA) or hydrogen peroxide to produce the corresponding compound in which the nitrogen of the pyridine ring is as an N-oxide:

wherein one of a', b', c' or d' is NeO and the others are CH or CR1 or
CR2. This reaction is normally run at temperatures from -15 C to reflux, more typically at about 0 C. The reaction is preferably conducted in an inert solvent such as methylene chloride for MCPBA or acetic acid for hydrogen peroxide.

The azaketone N-oxide of Formula 470.00a can then be reacted with a chlorinating agent such as SO2Cl2 or SOCIO to form a compound of
Formula 470.00b. Typically, this reaction results in monosubstitution of Cl in the ortho or para-position relative to the N atom of the ring.

To provide the disubstituted products, steps 1 and 2 above are repeated.

Typically, the resulting disubstituted compounds have Cl ortho and para relative to the N atom of the pyridine ring.

The mono or disubstituted compounds of Formulas 470.00b and 470.00c above can be reacted with various nucleophiles such as alkoxides, amines, thiols, etc. This will result in compounds where one or both of the Cl substituents are replaced by the nucleophile to provide a compound of Formula 470.00d or a compound easily converted to
Formula 470.00d.

The substituted ketone of Formula 470.00 can then be converted to the desired compound by the methods described above and in WO 88/03138 and in U.S. Patent No. 3,326,924.

Formula 405.00, wherein R1 or R2 are chlorine, can be made by the following alternate process.

The N-oxide of Formula 415.00 can be treated with POCK3 to form a compound of Formula 415.01. Typically, this reaction results in monosubstitution of Cl in the ortho or para position relative to the N atom of the ring.

Alternatively, the Cl substituted azaketones of Formula 470.00b or 470.00c above can be converted to the corresponding derivatives of
Formula 405.00 above wherein R1 and/or R2 is Cl by methods analogous to those described above. At this point the Cl substituent(s) can be displaced by an appropriate nucleophile to provide the desired substituent. Suitable nucleophiles include alkoxide, amines, thiols, etc.

This reaction usually requires higher tempertures (e.g., from about 1000 to about 2000C) than the displacement reaction to produce ketone 470.00d above. It is also usually conducted in a sealed vessel in an inert solvent.

The compound of Formula 405.00 is then converted to a compound of Formula 400.00 as described above.

Various electrophilic species can also be added to the pyridine ring from the corresponding halo-substituted pyridine (Formula 405.00 wherein R1 is halo, preferably bromo or iodo). Transmetallation of the halo derivative using an alkyl lithium (e.g. n-BuLi) provides the lithio derivative, which can then be quenched with the appropriate electrophile (e.g. R1L, etc.).

An alternative process for introducing substituents at the C-3 position of pyridine Ring I of Formula 1.0, involves nitrating a compound of Formula 415.00 (except wherein X is nitrogen) or a compound of Formula 470.00d with tetrbutylammonium nitrate - trifluoroacetic anhydride in methylene chloride at a temperature of 0 C to room temperature (about 25"C). The nitro group may then be reduced to the corresponding amine using iron filings in ethanol, or powdered zinc acetic acid in aqueous THF. By methods know to those skilled in the art, the amine group can be converted to a variety of substituents, such as, halo, cyano, thio, hydroxyl, alkyl, alkenyl, alkynyl and haloalkyl.

Wherein Z represents sulfur, a compound of Formula 400.00 wherein Z is oxygen is reacted with P2S5, Lawesson's reagent, or another reagent capable of introducing sulfur in place of oxygen. The reaction may take place at elevated temperature in pyridine, toluene or other suitable solvents. In this and other reactions, numerous conversions of a compound of Formula 400.00 (Z = 0) to another compound of Formula 400.00 (Z = S) are possible.

PREPARATION OF C5-C6-ENE DERIVATIVES
Compounds of formula 400.00 with a double bond between C-5 and C-6 can be prepared by heating a compound of Formula 470.00h in acetic acid with SeO2 to produce a compound of Formula 470.00i.

Compounds of Formula 470.00i can be converted to final products according to methods already described.

PREPARATION OF PIPERAZINE ANALOGS
Compounds having a piperazine ring bound to the C-1 1 of the tricyclic nucleus, i.e., Formula 1.0 wherein X is N, are best prepared via alkylation of the appropriately substituted piperazine compound of Formula 700.00 with a compound of Formula 705.00. Compounds of Formula 705.00 contain the appropriately substituted halide (such as Cl, Br, or I) or other similar leaving group (e.g., tosyloxy or mesyloxy). The reaction is usually conducted in an inert solvent, such as THF or toluene, optionally with a base such as triethylamine or potassium carbonate, and typically at a temperature range of ambient to reflux to produce a compound of Formula 710.00.

In this reaction Rg is H, CO2Ra (wherein Ra is a C1 to C4 alkyl group) or C(Z)R. The preparation of compound 705.00 wherein L is Cl is analogous to the procedure described in U.S. 3, 409,621. One skilled in the art can prepare other derivatives of 705.00 (e.g., L is Br, I, mesyloxy, or tosyloxy).

When Rg is H, C(Z)R or CO2Ra, these are converted to compounds of the invention by processes known in the art.

An alternate route for generating the compound of Formula 710.00 is by reductive amination of the aza ketone 715.00 with the piperazine 700.00

The reaction is typically carried out in a polar solvent, such as methanol or ethanol, optionally in the

presence of a dehydrating agent, such as 3A molecular sieves. The intermediate Schiff base can be reduced to the compound of Formula 710.00 by employing a variety of reducing agents, such as NaCNBH3, or catalytic hydrogenation, for example, hydrogen over Pd/C.

When Rg is C(Z)R, these are the compounds of the invention.

When Rg is H or CO2Ra, these are converted to compounds of the invention as described herein.

Compounds of Formulas 5.3A and 5.3B, wherein R25 represents a pyridyl N-oxide, can be produced by reacting compounds of Formulas 5.3A and 5.3B, wherein R25 is pyridyl, with a one molar equivalent of an oxidizing agent (such as oxone).

Compounds of Formulas 5.3, 5.3A and 5.38, wherein R25 represents a pyridyl N-oxide, can be produced by reacting the product of
Preparative Example 12 with a peroxyacid (such as m-chloroperbenzoic acid) to give the corresponding N-oxide intermediate. The desired Noxide product may be obtained from the N-oxide intermediate by following the procedure of Example 183.

In the above processes, it is sometimes desirable and/or necessary to protect certain R1, R2, R3 and R4 etc., groups during the reactions.

Conventional protecting groups are operable as described in Greene,
T.W., "Protective Groups In Organic Synthesis," John Wiley & Sons, New
York, 1981. For example, the groups listed in column 1 of Table 1 may be protected as indicated in column 2 of the table:
TABLE 1
PROTECTED GROUPS

FI1. GROOP TO BE PROTECTED I 2. PROTECTED GROUP
-COOH00alkyl, -C00benzyl,
j 00phenyl,
)NCObenzyr,
NCOalkyl,
,NH)phenyl
¦ -OH zoo , -OCH2phenyl,
-OH 0
-OCH3 , -OH3, OSi(CH3)2(t-Bu),
¦ -N-, wherein R is any
substituent on an amino
group within the scope of I R
the claims I O
-NR-CO-CF, -NRCOCH3,
1 -NRCH2Q
-NH2
0
-NH-C(O)-O(t-Bu)

Other protecting groups well known in the art also may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 1
A. N-(1 .1 -DI METHYLETHYL)-3-METHYL-2-PYRIDINE
CARBOXAMIDE

Suspend 2-cyano-3-methyl pyridine (400 g) in t-butanol (800 mL) and heat to 700C. Add concentrated sulphuric acid (400 mL) dropwise over 45 minutes. Maintain the temperature at 750C, until the reaction is complete, and for an additional 30 minutes. Dilute the mixture with water (400 mL), charge with toluene (600 mL) and bring to pH 10 with concentrated aqueous ammonia. Maintain the temperature at 50-550C during the work up. Separate the toluene phase, and reextract the aqueous layer. Combine toluene phases and wash with water. Remove the toluene to yield the title compound N-(i , 1 -dimethylethyl)-3-methyl-2- pyridine carboxamide, as an oil, from which solid product is crystallized.

(Yield 97%, as determined by an internal standard assay with gas chromatography).

B. 3-t2-(3-CHLOROPH ENYL)ETHYLi-N-(1 .1 -DIMETHYL ETHYL)-2-PYRIDINE CARBOXAMIDE

Dissolve the title compound of Preparative Example 1A, N-(1,1dimethylethyl)-3-methyl-2-pyridine carboxamide (31.5 g.) in tetrahydrofuran (600 mL) and cool the resulting solution to -400C. Add nbutyllithium (2 eq.) in hexane while maintaining the temperature at - 40"C.

The solution turns deep purple-red. Add sodium bromide (1.6 g) and stir the mixture. Add solution of m-chlorobenzylchloride (26.5 g., 0.174 mole) in tetrahydrofuran (125 mL) while maintaining the temperature at -400C.

Stir the reaction mixture until the reaction is complete as determined by thin layer chromatography. Add water to the reaction until the color is dissipated. Extract the reaction mixture with ethyl acetate, wash with water, and concentrate to a residue which is the title compound. (Yield 92% as shown by chromatography).

C. 3-[2-(3-CHLOROPHENYL)ETHYL]-2-PYRIDINE-CARBO-NITRILE

Heat a solution of the title compound of Preparative Example 1B, 3 [2-(3-chlorophenyl)ethyl]-N-(I ,1 -dimethylethyl)-2-pyridine carboxamide (175 g, 0.554 mole) in phosphorous oxychloride (525 mL, 863 g, 5.63 mole) and reflux for 3 hours. Determine completion of the reaction by thin layer chromatography. Remove any excess phosphorous oxychloride by distillation at reduced pressure and quench the reaction in a mixture of water and isopropanol. Bring to pH 5-7 by adding 50% aqueous sodium hydroxide solution while maintaining the temperature below 30"C. Filter the crystalline slurry of crude product and wash with water. Purify the crude product by slurrying the wet cake in hot isopropanol, and cool to 050C. Filter the product, wash with hexane and dry at a temperature below 500C to yield the title compound. (Yield: 1189 (HPLC purity 95.7%), m.p.

720C-730C, 89.4% of theory).

D. 1-(METHYL-4-PIPERIDINYL)[3-(2-(3-CHLORO PHENYL)ETHYL)-2-PYRI DI NYL)METHANONE HYDROCHLORIDE

Dissolve the title compound of Preparative Example 1C, (118 g, 0.487 mole) in dry tetrahydrofuran (1.2L) and add N-methyl-piperidyl magnesium chloride (395 mL, 2.48 mole/liter, 0.585 mole, 1.2 eq.) over 15 minutes. Maintain the temperature at 400C-500C by cooling with water as necessary, for 30 minutes. Determine completion of the reaction by thin layer chromatography. Quench the reaction by reducing the pH to below 2 with 2N HCl and stir the resulting solution at 250C for 1 hour. Remove the bulk of the tetrahydrofuran by distillation and adjust the resulting solution to pH 3.5 by addition of aqueous sodium hydroxide. Cool to 0 to 5"C and filter off the crystalline hydrochloride salt product. Wash with ice cold water and dry to constant weight at 600C to yield the title compound.

(Yield: 168.2 g (HPLC purity 94%), m.p. 1830-185"C, 89% of theory).

E. 8-CHLORO-11-(1-METHYL-4-PIPERIDYLIDENE)-6,11 DI HYDRO-5H-BENZO[5.6ICYCLOHEPTAF1 .2-biPYRI DINE

Dissolve the title compound of Preparative Example 1D above (59 g, 0.15 mole) in hydrofluoric acid (120 mL, 120 g, 6.0 mole) at -350C and add boron trifluoride (44.3 g, 0.66 mole) over 1 hour. Determine completeness of the reaction by thin layer chromatography. Quench the reaction using ice, water and potassium hydroxide bringing the solution to a final pH of 10. Extract the product with toluene and wash with water and brine. Concentrate the toluene solution to a residue, and dissolve in hot hexane. Remove the insolubles by filtration and concentrate the filtrate to yield the title compound as an off-white powder. (Yield: 45.7 g (HPLC purity: 95%), 92% of theory).

Alternative Step E: 8-CH LORO-1 1 -(1 -METHYL-4- PIPERIDYLIDENE)-6. 11 -DI HYDRO-5H-BENZOtS.6ICYCLOHEPTA(1 .2- b]PYRIDINE
React the title compound of Preparative Example 1D above (177 g, 0.49 mole) in trifluoromethanesulfonic acid (480 ml, 814.1 g, 5.31 mole) at 90-95"C for 18 hours under nitrogen. Determine the completeness of the reaction by thin layer chromatography. Cool the reaction and quench the reaction with ice-water and adjust the pH to 6 with barium carbonate.

Extract the product with methylene chloride, and concentrate under reduced pressure to about 1 liter. Wash with water, and extract the product into 1 N HCI which is treated with 30 g of activated charcoal, and filter through celite. Adjust the pH of the filtrate to 10 with aqueous sodium hydroxide (50%), extract the product into methylene chloride, and remove under reduced pressure to form a residue. Dissolve the residue in hot hexane, and filter to remove insolubles. Concentrate the filtrate to yield the title compound as a beige powder. (Yield: 126 g (HPLC purity 80%), 65% of theory).

F. 8-CHLORO-1 1 -(1 -ETHOXYCARBONYL-4- PIPERIDYLIDENE)-6. 11 -DIHYDRO-5H-BENZO[S.6] CYCLOHEPTAFI .2- biPYRIDINE

Dissolve the title compound of Preparative Example 1 E above (45.6 g, 0.141 mole) in toluene (320 mL) at 800C and to it gradually add ethyl chloroform ate (40.4 mL, 45.9 g, 0.423 mole). Following complete addition, maintain the temperature at 800C for 1 hour, then add diisopropylethylamine (2.7 mL, 2.00 g, 0.016 mole) and additional ethyl chloroformate (4.1 mL, 4.65 g, 0.0429 mole). Monitor completeness of the reaction by thin layer chromatography. Upon completion, cool the reaction mixture to ambient temperature, and wash the toluene solution with water. Concentrate the organic layer to a residue and dissolve in hot acetonitrile (320 mL). Decolorize the solution with 14 g of activated charcoal. Remove the activated charcoal by filtration and concentrate the filtrate to a crystalline slurry. Cool the mixture to 0-50C, and isolate the product by filtration. Wash with cold acetonitrile and dry the product at below 70"C to yield the title compound. (Yield: 42.4 g (HPLC purity 97.4%), 80% of theory).

G. 8-CHLORO-11-(4-PIPERIDYLIDENE)-6.11-DIHYDRO-5H BENZOt5.6iCYCLOHEPTA[1 .2-b] PYRIDINE

Hydrolize the title compound of Preparative Example 1F, 8-chloro 11(1 -ethoxycarbonyl-4-piperidylidene)-6, 11 -dihydro-5H- benzo[5,6]cyclohepta[1 ,2-b]pyridine (39 g, 0.101 mole) with KOH (50 g) in ethanol (305 mL) and water (270 mL) at reflux under an argon atmosphere for 64 hours. Partially distill off the ethanol and dilute the residue with brine, and extract with ethyl acetate (3x). Wash the combined organic phases with water and dry with Na2 SO4. Remove the solvent to give a solid which can be recrystallized from toluene to give the title compound as a white solid. (Yield: 24.5 g, 77%, melting point 154 1 550C).

H. By substituting in step 18 above, the benzylic halide:

for meta-chlorobenzylchloride, and employing basically the same methods as steps C through G, the compound

is prepared. Dichloro compound (I) is recrystallized from toluene and has a melting point of 150-152"C. Reaction times are determined by TLC or
HPLC. In some instances purification of the product by chromatography is necessary.

PREPARATIVE EXAMPLE 2
A. N-(1.1-DIMETHYLETHYL)-3-[2-(4-FLUOROPHENVYL) ETHYLj-2-PYRIDINE CARBOXAMIDE

Cool a solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridine-
carboxamide (38.4 g, 0.2 mole) in dry THF (250 mt) to -400C and add n
butyl lithium (185 mL, 0.44 mole). Add sodium bromide (1.9 g, 18 mmol.) and stir for 15 minutes. Add 4-fluorobenzylchloride (31.8 g, 0.22 mole) and stir for 2.5 hours while warming to -50C. Quench the reaction with water and extract the product twice with ethyl acetate, then wash with brine (2X). Dry the organic phase over Na2SO4, filter and remove the solvent to give the title compound. (60.0 g, Yield 99%, m.p. 59-610C.)

B. 3-[2-(4-FLUOROPHENYL)ETHYU-2-PYRIDI NE
CARBONITRILE

Heat the title compound of Preparative Example 2A above (60.0 g, 0.2 mole) in POCl3 (200 mL) to 1100C under an argon atmosphere for 3.5 hours. Pour the reaction mixture onto ice and basify with NaOH (50%) solution. Extract the mixture with ethyl acetate (3x) and wash with water.

Wash with brine and dry over Na2 SO4. Remove the solvent and pass the residue through a coarse SiO2 (60-200 mesh) column to give the title compound as a white solid (40 g, Yield 88%, m.p. 48- 49 C.).

C. 9-FLUORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO-OHEPTA [1 .2-biPYRIDIN-1 1-ONE

Cyclize the title compound of Preparative Example 2B above (31.5 g, 139 mmol) in polyphosphoric acid (1.24 kg) at 200 C for 5.5 hours.

Pour onto ice and basify with NaOH solution (50%). Extract the product with chloroform (3x) and wash with brine. Dry the organic phase with
Na2SO4, filter and remove the solvent to give the title compound (20.4 g, yield 64%, m.p. 78-81 C after recrystallization from diisopropyl ether).

D. 9-FLUORO-11-(1-METHYL-4-PIPERIDINYL)-6.11 DIHYDRO-SH-BENZOTS G1CYCLOPHEPTAI1 .2-blPYRIDIN-11-OL

Dissolve the title compound of Preparative Example 2C above (10.0 g, 44 mmol) in THF (100 mL) and add slowly to a cooled (-40 C) solution of the Grignard reagent prepared from N-methyl-4-chloropiperidine (57.9 mL, 88 mmol) and magnesium in THF (70 mL). Stir the mixture for about 1 hour while warming up to OOC. Quench the reaction with NH4Cl solution and extract with ethyl acetate (2X). Wash the organic phase with brine and dry over Na2SO4, filter and remove the solvent.

Purify the residue with flash chromatography and elute with methanol (5%) in CHCl3 to give the title compound as white granular crystals. (10.1 g, Yield 70%, m.p. 126-127"C after recrystallization from diisopropyl ether.)

E. 9-FLUORO-1 1 -(1 -METHYL-4-PIPERIDYLENE)-6. 11
DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

Add the title compound of Preparative Example 2D above (7.3 g, 22.3 mmol) to a mixture of cooled H2SO4 and CF3SO3H(1:1),(146mL).

Stir the reaction mixture for 0.5 hours at ice bath temperature and then at room temperature for 1.5 hours. Pour the reaction mixture onto ice and basify with NaOH (50%) solution. Extract the product with ethyl acetate (3X) and wash with brine. Dry the organic phase over Na2SO4, filter and remove the solvent to give a crude oil. Charcoal the oil and recrystallize from ethyl acetate and isopropyl ether to give the title compound. (5.6 g,
Yield 82%, m.p. 13.5-135.5 C.).

F. 9-FLUORO-11-(1-ETHOXYCarbonyl-4
PIPERIDYLIDENE)-6.11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2 blPYRIDINE

Stir a solution of the title compound of Preparative Example 2E above (5.0 g, 16.2 mmol) and triethylamine (2.6 g, 26 mmol) in dry toluene (60 mL) at 80"C under an argon atmosphere, and add ethyl chloroform ate (9.8 g, 90 mmol) via a syringe. Stir the reaction at this temperature for 30 minutes and at room temperature for one hour. Filter the reaction and remove the solvent. Pass the residue through a coarse SiO2 column (60200 mesh), and elute with CHCl3 to yield the title compound as a white solid. (4.5 g, Yield 76%, m.p. 112-114"C after trituration with pentane).

G. 9-FLUORO-11-(4-PIPERIDYLIDENE)-6.11-DIHYDRO-5H BENZO[5.6]CYCLOHEPTA[1 .2-b] PYRIDINE

Reflux the title compound of Preparative Example 2F above (3.83 g, 10.4 mmol) with KOH (4.6 g) in 50 mL of ethanol/H2O (1:1) for 4 hours under an argon atmosphere. Pour the reaction mixture into a brine solution and extract with ethyl acetate (2X), dry over Na2SO4 and filter.

Remove the solvent to give the title compound (2.86 g, Yield 90%, m.p.

138-140 C.).

H. By employing the benzyl halide

in place of 4-fluorobenzyl chloride in step 2A above, the product

is prepared (m.p. 138-140"C, triturated with pentane) by employing basically tha same process as described in steps 2A-2G. Workup time is determined by either TLC or HPLC. In some instances purification of the product by chromatography is necessary.

PREPARATIVE EXAMPLE 3
A. 3.5-DIMETHYLPYRIDINIUM N-OXIDE

A solution of 285 mL (1.31 mol) of 35% peracetic acid was slowly added to a stirred solution of 149 g (1.39 mol) of 3,5-dimethylpyridine during which the temperature rose to 850C and was maintained at this temperature during addition. After the temperature of the mixture dropped to about 35"C the reaction was stored at 50C overnight.

After partial removai of 185 ml of acetic acid via distillation under vacuum, the reaction was washed with NaHSO4 solution and then neutralized with 10% NaOH solution to pH of about 7. The product was extracted with CH2Cl2 to give the title compound as a white solid (yield 142 g, 83%).

B. 1 -METHOXY-3.5-DIMETHYLPYRIDINIUM METHYL SULFATE

Dimethylsulfate (42.0 g, 0.33 mol) was slowly added to 41.0 g (0.33 mol) of 3,5-dimethylpyridinium N-oxide with mechanical stirring. The mixture was then heated on a steam bath for 1 hr. Then vacuum was applied while cooling to give a brownish solid of the title compound in quantitative yield.

C. 2-CYANO-3.5-DIMETHYLPYRIDINE

To a cooled (00C) solution of sodium cyanide (49.0 g, 0.999 mol, 3.0 eq.) in 135 mL of water (air free) was dripped 1-methoxy-3,5-dimethyl pyridinium methyl sulfate (83.0g, 0.33 mol) in 100 mL water (air free) in 1.25 hr., keeping the temperature below 3 C. The reaction mixture was stored at about 3"C overnight. The mixture was filtered and washed with water to give 40g of the title compound. An analytical sample was recrystallized from isopropyl ether and pentane (4:1) (m.p.: 61-62 C).

D. N-(1 .1 -DI METHYLETHYL)-3.5-DI METHYL-2-PYRIDINE CARBOXAMIDE

To a stirred solution of 20.3 g (0.153 mol) of 2-cyano-3,5dimethylpyridine in 100 mL of 20 mL of conc. sulfuric acid within 10 minutes, followed by 20 mL of t-butanol over an additional 15 minutes.

The solution was warmed at 750C for 30 minutes after which it was cooled to room temperature and basified with 25% NaOH. The product was extracted 3X with EtOAc (600 mL), which was combined and washed 1X with brine, dried (Na2SO4), filtered and concentrated in vacuo to give the title compound (31.26 g) as a yellowish oil.

E. 8-CHLORO-3-METHYL-11-(4-PIPERIDYLIDENE)-6,11 DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

By substituting in step 1B above N-(1,1-dimethylethyl)-3,5-dimethyl- 2-pyridine carboxamide for N- (1,1 - dimethylethyl)-3-methyl-2-pyridine carboxamide and employing basically the same methods as steps B through G of Preparative Example 1, one obtains 8-chloro-3-methyl-l 1-(4- piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Reaction times are determined by TLC or HPLC.

PREPARATIVE EXAMPLE 4
By substituting

for 3,5-dimethylpyridine in Preparative Example 3 above and following basically the same procedure (steps A-E), the compounds

respectively, can be prepared. Note that the addition of the nitrile group to the pyridine in Step C of Preparative Example 3 can result in the formation of other undesirable isomers which can be removed via flash chromatography.

PREPARATIVE EXAMPLE 5
A. 8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA [1.2-b]PYRIDIN-11-ONE N-OXIDE

To a mixture of 25.1 grams (0.103 mole) of 8-chloro-S,6-dihydro- 11H-benzo[5,6]cycloheptal[1,2-b]pyridin-11-one in 175 ml of dry methylene chloride at OOC under an argon atmosphere was added dropwise over 70 minutes a solution of 24.12 grams of 3-chloroperoxybenzoic acid in 150 ml of methylene chloride. After the addition the solution was stirred for 1/2 hour after which the ice bath was removed.

After two days the reaction was poured into 1.0 N aqueous sodium hydroxide and extracted with methylene chloride. The organic portions were combined, washed once with water, dried over magnesium sulfate, filtered and concentrated in vacuo. The resultant product was triturated with isopropyl ether and filtered to provide 25.8 grams (96%) yield of the title compound.

B. 2.8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE AND 4.8-DICHLORO-5,6 DIHYDRO-1 1 H-BENZO[S.G1CYC LOH EPTAI1 .2-bIPYRI DI N-I 1 -ONE

To a mixture of 29.13 grams (112.2 mmol) of the title compound from Preparative Example 5A above, in 40 ml of dry methylene chloride at 0 C and under argon atmosphere was added 500 ml of 1.0 M SO2C12 dropwise over 1 hour. The ice bath was then removed and the reaction stirred at room temperature for 1 hr and then refluxed for seven hours.

The mixture was poured into 1.0 N aqueous NaOH and extracted three times with CH2C12. The organic portions were combined, dried over Mg SO4, filtered and concentrated in vacuo to yield a product which was purified and separated via flash chromatography to yield the two title compounds.

C. 4-(2.8-DICHLORO-5.6-DIHYDRO-1 1 H-BENZO[5.6]- CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)PIPERIDINE AND 4-(4,8 DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA-[1,2-b] PYRIDIN-11-YLIDENE)PIPERIDINE

By following essentially the same procedure as that described in parts D-G of Preparative Example 2 above, the 2,8-dichloro and 4,8dichloro products of Preparative Example 5B above were converted to the corresponding title compounds.

PREPARATIVE EXAMPLE 6
A. 3-(1.1-DIMETHYL-1-ETHYL)-8-CHLORO-5,6-DIHYDRO11H-BENZO[5,6]CYCLOHEPTA[1,2-b] PYRIDIN-11-ONE

To a mixture of 20.05 grams (82.28 mmol) of 8-chloro-5,6-dihydro11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one in 400 ml of dry tetrahydrofuran at -720C and under an atmosphere of nitrogen was added dropwise over 40 minutes 66.0 ml of 2.7 M t-butyl magnesium chloride in tetrahydrofuran. The reaction mixture was slowiy warmed to room temperature and stirred overnight. The mixture was then poured into 10% aqueous ammonium chloride and extracted four times with methylene chloride. The combined organic portions were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the title compound, along with 8-chloro-11-(1,1-dimethyl-1-ethyl)-6,11-dihydro-5H benzo[5,6]cyclohepta[1,2-b] pyridin-11-ol. These compounds were separated via flash chromatography to give the title compound, which was recrystallized from isopropyl ether to give 4.37 grams (18%) of the title compound as a white solid.

B. 4-(3-(1.1 -DI METHYL- 1 -ETHYL)-8-CHLORO-5.6-DI HYDRO- 11H-BENZO[5,6]CYCLOHEPTA[1,2-b] PYRIDIN-11-YLIDEND]PIPERIDINE

By using the title compound of Part A above and applying essentially the same procedure described in parts D-G of Preparative
Example 2 above, one can obtain the title compound.

PREPARATIVE EXAMPLE 7
A. 8-CHLORO-6. 11 -DI HYDRO-1 1 -HYDROXY-SH-BENZO[5.6]- CYCLOHEPTAF1 .2-b]PYRIDINE

To a mixture of 25.03 g (103 mmol) of 8-chloro-5,6-dihydro-11H- benzo[5,6]cyclohepta[1 ,2-b]pyridin-l l-one in 200 mL of methanol at room temperature and under a nitrogen atmosphere was added portionwise over a period of about 1 hour 4.82 g (124 mmol) of sodium borohydride.

Occasional cooling with an ice bath was necessary at times during the addition in order to avoid excessive reflux. After 1.6 hours the mixture was poured into ice cold water and then extracted with ethyl acetate (3X). The combined organic portions were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was recrystallized from hot isopropyl ether. The remaining filtrate was purified via flash chromatography (20% ethyl acetate in hexanes) to yield more product which solidified on standing. Both batches were combined to yield 20.41 g of the title compound as a white solid.

B. 8.11-DICHLORO-6.11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTAtI .2-b]PYRIDINE

To a mixture of 13.3 g (54 mmol) of 8-chloro-6,1 1-dihydro-1 1- hydroxy-5H-benzo[5,6]cyclohepta[1,2-b] pyridine in 290 mL of toluene at -15 C and under an atmosphere of nitrogen was added via syringe pump over a period of 1 hour 6.20 mL (85.7 mmol) of thionyl chloride.The extent of reaction was monitored by TLC (50% ethyl acetate in hexanes). When completed the mixture was poured into 300 mL of 1.0 N aqueous sodium hydroxide and extracted with ethyl acetate (5X). The combined organic portions were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in ethyl acetate, quickly filtered through basic alumina, and concentrated again to yield a product which was triturated with pentane to yield 10.22 g of the title compound as a tan solid.

C. 8-CHLORO-11-(1-PIPERAZINYL)-6.11-DIHYDRO-5H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

To a mixture of 10.0 g (37.9 mmol) of 8,11-dichloro-6,11-dihydro- 5H-benzol5,6]cyclohepta[1,2-b]pyridine

and 1.0 mL of triethylamine in 200 mL of dry tetrahydrofuran at room temperature and under a nitrogen atmosphere was added 33.0 g of piperazine. The mixture was stirred at room temperature for 22.5 hours and then refluxed for 5.5 hours. It was then cooled to room temperature, poured into 250 mL of 5% aqueous sodium hydroxide, and extracted with methylene chloride (3X). The combined organic portions were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (2e5% methanol saturated with ammonia in methylene chloride) to yield the title compound as a glass.

PREPARATIVE EXAMPLE 8
A. ETHYL 3-PYRIDYLACETIC ACID I-N-OXIDE

Ethyl 3-pyridylacetic acid (grams) (60.6 mmoles) was dissolved in dry dichloromethane (120ml) and the solution was stirred at -180C for 30 minutes. 3-Chloroperbenzoic acid (31.34 grams) (181.6 mmoles) was added and the mixture was stirred at -180C for 1 hour and then at 250C for 87 hours. The reaction mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and then water. The dichloromethane was then dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% concentrated ammonium hydroxide in methanol)dichloromethane as the eluant to give the title compound (Yield: 8.45 grams, 77%, MH+ 182).

B. 3-PYRIDYLACETIC ACID 1-N-OXIDE

3-Pyridylacetic acid (0.2747 grams) (1.5 mmoles) was dissolved in ethanol (200 proof) (1.22 ml.) and a 1 M solution of lithium hydroxide in water (3.64 ml.) (3.0 mmoles) was added and the mixture was stirred at 250C for 4 hours. 1 N Hydrochloric acid (4.28 ml.) was added and the mixture was pumped down to dryness on a rotary evaporator to give the title compound (Yield: 0.2931 grams, 100%).

PREPARATIVE EXAMPLE 9
A. ETHYL oe-METHYL-3-PYRIDYLACETIC ACID.

To ethyl 3-pyridylacetic acid (10.86 grams) (65.7 mmoles) was added a 2.0M solution of lithium diisopropylamide in THE / heptane / ethyl benzene (32.87 ml.) (65.8 mmoles) at -300C. The semi-solid mixture was agitated and sonicated for 1 hour. The mixture was allowed to remain at 250C for 1 hour, whereupon methyl iodide (4.09 ml.) (65.7 mmoles) was added. After 1 hour at 250C the mixture was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate and water. The dichloromethane was dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as the eluant to give the title compound (Yield: 3.48 grams, 30%, MH+ 180).

B. a-METHYL-3-PYRIDYLACETIC ACID.

The title compound from Preparative Example 9A above (2.16 grams) (12.05 mmoles) was dissolved in ethanol (10 ml.) and 1.0M lithium hydroxide in water (29.15 ml.) (29.2 mmoles) was added. The mixture was stirred at 250C for 4 hours, whereupon 1N hydrochloric acid (34.27 ml.) (34.2 mmoles) was added and the solution was evaporated to dryness to give the title compound (Yield 2.33 grams, 100%).

PREPARATIVE EXAMPLE 10
, -DIMETHYL-3-PYRIDYLACETIC ACID.

Ethyl a,a-dimethyl -3-pyridylacetate (disclosed in EP Application 0 288 279, published October 26, 1988) (2.67 grams, 13.8 mmoles) was dissolved in ethanol (11.1 ml.) and a 1.OM lithium hydroxide in water (33.3 ml.) (33.4 mmoles) was added. The mixture was stirred at 250C for 4 hours. 1N Hydrochloric acid (38.73 ml.) was added and after 5 minutes the mixture was evaporated to dryness to give the titile compound (Yield: 100%).

PREPARATIVE EXAMPLE 11 A. 8-C H LORO-6, 1 1 -DI HYDRO-I 1 -(1 -PIPERAZINYL)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE 1-N-OXIDE

To a mixture of 8-chloro-5,6-dihydro-1 1 H-benzo[S,6]cyclohepta- [1,2-b]pyridin-11-one (5 grams) (20.6 mmoles) in dry dichloromethane (35 ml) was added dropwise 3-chloroperbenzoic acid (4.7 grams) (27.3 mmoles) in dry dichloromethane (75 ml) at 0-25 C over 1 hour. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and water. The dichloromethane was dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 1% (10% saturated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (Yield: 2.81 grams, 53%, MH+ 260).

B. 8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA [1,2-b]PYRIDIN-11-OL1-N-OXIDE

By using the title compound (8.6 grams) from Preparative Example 11A and reducing it by the procedure described in Preparative Example 7A above the title alcohol was obtained (Yield: 7.03 grams, 81%, MH+ 262).

C. 8.11-DICHLORO-6.11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTA(1 .2-b]PYRIDINE 1-N-OXIDE

The title compound from Preparative Example 11 B (6.2 grams) (23.7 mmoles) was reacted with thionyl chloride as described in
Preparative Example 7B to give the title compound.

D. 8-CHLORO-6,11-DIHYDRO-11-(1-PIPERAZINYL)-5H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE 1-N-OXIDE

The title compound from Preparativ eExample 11C above was reacted with piperazine (9.9 grams) (115.0 mmoles) as described in
Preparative Example 7C to give the title compound (Yield: 6.78 grams, 87%, MH+ 330).

PREPARATIVE EXAMPLE 12 4-ETHOXYCARBONYLAMINOPYRIDINE

4-Aminopyridine (17.34 grams) (184.3) was dissolved in dry pyridine (217 ml.) and cooled to OOC over 30 minutes. Ethyl chloroformate (17.2 ml.) (180.7 mmoles) was addedand the solution was stirred at OOC for 1 hour and then at 250C for 40 hours. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and water. The dichloromethane was dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2% (10% saturated ammonium hydroxide in methanol)-dichloromethane to give the title compound (Yield: 10 grams, 33%, M+ 166).

By using essentially the same procedure, with the exception that

was used instead of 4-aminopyridine, the compound

Amorphous Amorphous
solid, MH+ 167 or solid, MH+ 167 was obtained, respectively.

PREPARATIVE EXAMPLE 13
A. N-ACETYLISONIPECOTIC ACID

Isonipecotic acid (10 grams) (77.5 mmoles) and acetic anhydride (23.7 grams) (232.5 mmoles) were dissolved in methanol (100 ml.) and the mixture was stirred at 250C for 24 hours. The mixture was evaporated to dryness and the residue was azeotroped with toluene to give the title compound (Yield: 12.8

grams, 97%, MH+ 172).

B. 1 -N-tert-BUTOXYCARBONYLISONIPECOTIC ACID

Isonipecotic acid (20 grams) (155.0 mmoles) was dissolved in THFwater (1:1) (400 ml) and sodium hydroxide (6.2 grams) (155.0 mmoles) and di-tert-butyldicarbonate (37.2 grams) (170.5 mmoles) were added.

The mixture was stirred at 250C for 72 hours. The solution was then eluted through a bed of washed BioRad 50WX4 (RSO3H resin) (150 ml bed) and the resin was eluted with a 1:1 mixture of THF and water. The eluate was evaporated to dryness to give the title compound (Yield: 33.78 grams, 90%).

PREPARATIVE EXAMPLE 14
1 -N-ACETYLNIPECOTIC ACID

Nipecotic acid (3.87 grams) (30.0 mmoles) was reacted with acetic anhydride (9.17 grams) (90 mmoles) as described in Preparative Example 13A to give the title compound (Yield: 5.0 grams, 97%, MH+ 172).

PREPARATIVE EXAMPLE 15
1-N-METHYLNIPECOTIC ACID

Arecaidine hydrochloride (4 grams) (22.6 mmoles) was hydrogenated in water (100 ml) using 10% Pd-C at 40 psi at 250C for 24 hours. The catalyst was filtered off and washed with water. The aqueous solution was shaken with BioRad AG1X8 resin (OH- form) (23 ml bed) and after 5 minutes the resin was filtered off and washed with water. The aqueous solution was evaporated to give the title compound (Yield: 2.95 grams, 92%).

PREPARATIVE EXAMPLE 16
1 -N-ACETYL D.L-PIPECOLINIC ACID

D,L-Pipecolinic acid (10 grams) (77.5 mmoles) and acetic anhydride (23.7 grams) (232.5 mmoles) were reacted as described in
Preparative Example 13A above to give the title compound (Yield: 12.94 grams, 98%, MH+ 172).

PREPARATIVE EXAMPLE 17
A. PIPERIDINE-4-ACETIC ACID

4-Pyridylacetic acid (7 grams) (40.4 mmoles) was hydrogenated as described in Preparative Example 15 to give the title compound (Yield: 5.2 grams, 90%, MH+ 144).

B. 1-N-ACETYL-4-PiPERIDINYLACETIC ACID

4-Piperidinylacetic acid (5 grams) (35.0 mmoles) was reacted with acetic anhydride (10.7 grams) (105.0 mmoles) as described in
Preparative Example 13A to give the title compound (Yield: 6.4 grams, 99%, MH+ 185).

C. 1 -N-METHYL-4-PIPERIDINYLACETIC ACID

4-Piperidinylacetic acid (4 grams) (28.0 mmoles) from Preparative
Example 17A was dissolved in water (50 ml) and 37% formalin (2.72 ml) (33.6 mmoles) was added. The mixture was hydrogenated over 10% Pd
C at 55psi at 25"C for 68 hours. The catalyst was filtered off and washed with water. The combined filtrates were evaporated to dryness to give the title compound (MH+158).

D. 1 -N-tert-BUTOXYCARBONYLPIPERIDINYL-4-ACETIC ACID

4-Piperidinylacetic acid (41.24 grams) (288.4 mmoles) from
Preparative Example 17A was reacted with di-tert-butyldicarbonate (69.14 grams) (317.3 mmoles) and sodium hydroxide (11.52 grams) (288.4 mmoles) as described in Preparative Example 1 3B above to give the title compound (Yield: 53.0 grams, 76%).

PREPARATIVE EXAMPLE 18
A. 3-PIPERIDINYLACETIC ACID

3-Pyridylacetic acid hydrochloride (13 grams) (74.9 mmoles) was hydrogenated as described in Preparative Example 15 to give a mixture of unreacted 3-pyridylacetic acid and the title compound (76:24) (8.63 grams, MH+ 144).

B. 1-N-ACETYL-3-PIPERIDINYLACETIC ACID

The mixture of compounds from Preparative Example 18A (8.56 grams) were reacted with acetic an hydride (8.56 grams) as described in
Preparative Example 13A and the crude mixture of products was taken up in methanol (60 ml) and passed over a bed of BioRad AG50WX4 resin (RSO3H) and the latter was eluted with methanol. The eluates were evaporated to dryness to give the title compound (Yield: 1.23 grams, MH+ 186).

C. I-N-METHYL-3-PIPERIDINYLACETIC ACID

The mixture of compounds from Preparative Example 18A (4 grams) and 37% formalin (2.72 ml.) were hydrogenated as described in
Preparative Example 17C to give the title compound (MH+ 158).

PREPARATIVE EXAMPLE 19
PREPARATION OF THE R(+) AND S(-) DIASTEREOISOMERS
The racemic 8-chloro-11-(1-piperazinyl)-6,11-dihydro-5H-benzo [5,6]cyclohepta[1 ,2-b)pyridine prepared in Preparative Example 7C above was resolved by the method described in Preparative Example 15 A-C, pages 116-118, of WO 92/00293, published January 9, 1992, to give the
R(+) and S(-) diastereoisomers:

PREPARATIVE EXAMPLE 20
A. 3-BROMO-8-CHLOBO-5,6-DIHYDRO-11H-BENZO[5,6]
CYCLOHEPTA[1,2-b]PYRIDIN-11-ONE

Cyclize 3-[2-(3-chlorophenyl)ethyl]-4-bromo-2-pyridine carbonitrile (10.7g, 32.8 mmol) in triflic acid (82 mL) at 600C for 2 hours and then at room temperature for 2 hours. Add 80 mL of 5N HCl carefully, then reflux in an oil bath (1200C) for 30 minutes. Cool the solution and pour into ice and basify with 25% NaOH solution. Extract the product with CH2Cl2 and wash with brine. Dry the organic layer with Na2SO4,filter and remove the solvent to give crude product (10.49). Purify the crude product with flash chromatography on silica gel and elute with 15% ethyl acetate-hexane to give the title compound as a white solid (9g ,27.95 mmol, Yield 85.2%
MH+ 322).

B. 8-CHLORO-3-METHOXY-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTAF1 .2-bjPYRIDIN-1 1-ONE

Dissolve the title compound of Preparative Example 20A (2.37g, 7.4 mmol) in dry methanol and add sodium metal (3.379, 180 mmol). the reaction is stirred overnight at room temperature. Reflux the reaction for 3 hours, cool to room temperature and extract with dichloromethane-water.

Dry the CH2Cl2 fraction and chromatograph on silica gel eluting with 50% EtOAc-hexanes to give the title compound as a light yellow solid(1.5g, Yield 72% MH+ 274).

C. 8-CHLORO-3-METHOXY- 11 -(-4-PIPERIDYLIDENE)-6.1 1 - DIHYDRO-5H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDINE

By substituting in Preparative Example 2 step D, 8-chloro-3methoxy-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one for 9-fluoro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-one and employing basically the same methods as steps D through H of Preparative Example 2, one obtains 8-chloro-3-methoxy- 11-(4- piperidylidene)-6, 11 -dihyd ro-5 H-benzo [S ,6]-cyclohepta[l ,2-b]pyridine as a white solid (MH+ 340).

PREPARATIVE EXAMPLE 25
A. ETHYL a-METHYL-4-PYRIDYL ACETIC ACID

To dry THF at -780C was added diisopropylamine(5.05g 48 mmol, 7mL) and then n-butyl lithium. The reaction mixture was stirred for 0.5 h and then ethyl 4-pyridyl acetic acid (7.85g, 46 mmol) was added, and after sirring for 0.5 h at that -78 C the reaction temperature was raised to room temperature. DMF (20 mL was added and the reaction mixture cooled to -78 C again. Methyl iodide(7.07g, 50.2 mmol, 3.15 mL) was added and the reaction mixture stirred at that temperature for 1 h and then at room temperature overnight. All the volatiles were then stripped off and the reaction mixture was partitioned between water-CH2Cl2. The aqueous phase was washed twice with CH2Cl2. The combined CH2Cl2 phases were dried and evaporated. The crude product was chromatographed on silica gel eluting with 80% ethyl acetate hexane to give the title compound (7.88g, MH+ 179).

B. o-METHYL-4-PYRIDYL ACETIC ACID

The compound from Preparative Example 25A was hydrolysed in a similar manner to Preparative Example 9B to give the title compound (MH+ 152).

PREPARATIVE EXAMPLE 26
A. , -DIMETHYL-4-PYRIDYL ACETIC ACID

By essentialy the same procedure as set forth in Preparative Example 10A-B, but using ethyl a-methyl-4-pyridylacetic acid (from Preparative Example 25) instead of ethyl pyridyl acetic acid the title compound was obtained as an oil (MH+ 166).

PREPARATIVE EXAMPLE 27 ETHYL 4-[4.8-DICHLORO-5.6-DIHYDRO-1 H-BENZO[5.6]CYCLO-HEPTAT1 .2-blPYRIDIN-11-YLI DENE1-1-PI PERIDINECARBOXYLATE and ETHYL 4-[2,8-DICHLORO-5,6-DIHYDRO-11H BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE CARBOXYLATE

To phosphorous oxychloride (256 mL) stirring at reflux was added dropwise a solution of the title compound (109 grams) from Example 231A dissolved in chloroform (850 mL). After stirring the resulting solution for an additional 20 minutes at reflux, the reaction mixture was cooled to room temperature and the chloroform removed in vacua. The resulting solution was cooled in an ice-water bath and to it was slowly added 1 N aqueous sodium hydroxide (850 mL) followed by 50% aqueous sodium hydroxide until the resulting mixture was slightly basic. Extraction with ethyl acetate, drying of the organic phase over anhydrous magnesium sulfate, concentration in vacuo, and purification by flash column chromatography provided the 4,8-dichloro product (27 grams, 23% yield, mp 141.6-145.6 C) and the 2,8-dichloro product (9 grams, 8% yield, 176.5-177.9 C).

PREPARATIVE EXAMPLE 28
4.8-DICHLORO-11-(4-PIPERIDYLIDENE)-6.11-5H-BENZO[5,6] CYCLOHEPTAII .2-biPYRIDINE

A solution of the 4,8-dichloro compound from Preparative Example 27 (2.6 grams) dissolved in absolute ethanol (50 mL) and concentrated hydrochloric acid (100 mL) was stirred at reflux for 48 hours. The reaction mixture was cooled in an ice-water bath and was made basic by addition of solid potassium hydroxide. Concentration in vacuo afforded a solid which was diluted with dichloromethane and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the title compound (2.0 grams, 93% yield, mp = 181.1-183.2 C).

PREPARATIVE EXAMPLE 29
ETHYL 4-r4.8-DI CH LORO- 5.6-DIHYDRO-1 1 H-BENZOF5 . 6ICYCLO-
HEPTA[1.2-b]PYRIDIN-11-YLI DENE1- 1 -PI PERI DI NE CARBOXYLATE. N
OXIDE

To a cooled (00C) solution of the 4,8-dichloro compound from
Preparative Example 27 (9.5 grams) dissolved in dichloromethane (300 mL) under N2 was added dropwise a solution of meta-chloroperoxy- benzoic acid (6.8 grams) dissolved in ethyl acetate (200 mL). The resulting mixture was washed with 1 N aqueous sodium hydroxide, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) using 100% ethyl acetate then 10% methanol-dichloromethane to afford the title compound (4.9 grams, 50%, MH+ 433).

PREPARATIVE EXAMPLE 30
ETHYL 4-t4-(2-AMINOETHYLTHIO)-8-CHLORO-5.6-DIHYDRO- 11H-BENZO[5,6]CYCLOHEPTA[1,2-b]
PYRIDIN-11-YLIDENE]-1
PIPERIDINE CARBOXYLATE

A mixture of the title compound from Preparative Example 29 (0.53 grams), 2-aminoethanethiol hydrochloride (0.74 grams) and absolute ethanol(15 mL) was stirred at reflux for 48 hours. The mixture was cooled to 250C, diluted with dichloromethane and washed with 1 N aqueous sodium hydroxide. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the title compound (0.5 grams, 88%, MH+ 458).

PREPARATIVE EXAMPLE 31
1,1-DIMETHYLETHYL [2-[8-CHLORO-6,11-DIHYDRO-11-(1 ETHOXYCARBONYL)-4-
PIPERIDINYLIDENE]-5H-BENZO[5.6]CYCLO-
HEPTA[I .2-bIPYRIDIN-4-YL1THIO1ETHYL1CARBAMATE

To the title compound from Preparative Example 30 (0.33 grams) dissolved in dichloromethane (60 mL) was added di-tert-butyldicarbonate (0.17 grams). The solution was stirred at 25"C under N2 overnight. An additional 0.1 grams of di-tert-butyldicarbonate was added and after 4 hours the reaction mixture was diluted with dichloromethane, washed with 1 N aqueous sodium hydroxide and concentrated in vacuo to afford the title compound (0.5 grams, 100%, MH+ 558).

PREPARATIVE EXAMPLE 32
1.1-DIMETHYLETHYL [2-[[8-CHLORO-6,11-DIHYDRO-11-[4
PIPERIDINYLIDENE]-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-4 YLiTHIO]ETHYL]CARBAMATE

To the title compound from Preparative Example 31 (0.22 grams) dissolved in absolute ethanol (5 mL) was added water (5 mL) and solid potassium hydroxide (0.33 grams). The solution was stirred at reflux for 4 days, then cooled to 250C, diluted with dichloromethane and washed with water. The organic phase was concentrated in vacuo and the residue purified by flash column chromatography (silica gel) using 5% methanoldichloromethane saturated with ammonium hydroxide to afford the title compound (0.04 grams, 19%, MH+ 486).

PREPARATIVE EXAMPLE 33
3-PYRIDYLISOCYANATE. HYDROCHLORIDE

A 1.93 solution of phosgene in toluene (20%) (584 mL) was diluted with dry dichloromethane (1 L) and the mixture was stirred at OOC under nitrogen atmosphere. A solution of 3-aminopyridine (21.1 grams) and dry pyridine (19 mL) dissolved in dry dichloromethane (600 mL) was added dropwise to the stirred solution at OOC over a period of 5.5 hours. The mixture was stirred at 0-250C for an additional 48 hours. A stream of nitrogen was passed through the solution to remove most of the phosgene and the solution was then evaporated until almost all of the solvent was removed to give the title compound which was then taken up in dry pyridine (850 mL) to give a stock solution of the title compound.

PREPARATIVE EXAMPLE 34
A. 8-CH LORO-I I -(1 -ETHOXYCARBONYL-4-PIPERIDINYL)- 11H-BENZO[5,6]CYCLOHEPTA(1,2-b) PYRIDINE
B. 8-CHLORO- 11 - (1 -ETHOXYCARBONYL-4-PI PERI DI NYL)-9- ETHYL 1 H-BENZO[S .6iCYCLOHEPTA(I .2-b)PYRIDINE

The title compound of Preparative Example 1F above (51.15 grams, 0.1336 mole) was dissolved in trifluoromethanesulfonic acid (170 mL). The dark mixture was heated to reflux for 70h. The solution was cooled to room temperature and was then poured into 800 mL of an ice/water slurry and the resulting mixture stirred. Concentrated ammonium hydroxide solution (175 mL) was added to the mixture in small portions so that the temperature of the mixture was below 200C. The resulting basic mixture was extracted with dichloromethane. The dichloromethane extract was washed with brine and was then evaporated to give a brown residue. This residue was dissolved in dichloromethane (750 mL) and the solution cooled to OOC. Ethyl chloroformate (14.8 grams, 0.136 mole) was added over 5 minutes and the resulting mixture stirred at 0o C for 15 minutes. Saturated sodium bicarbonate solution (150 mL) was added and the cooling bath was removed. The resulting biphasic mixture was stirred rapidly for 3h. The layers were separated and the dichloromethane layer was filtered through silica gel. The filtrate was evaporated to dryness and the residue chromatographed on silica gel using a gradient of hexane-dichloromethane-acetone 16:2.5:1.5 to hexane-dichloromethane-acetone 28:7.5:4.5 as eluent to give title compound A (25.029 49% MH+ 383) and title compound B (4.85g, 9%,
MH+ 411).

C. 8-CHLORO-1 I -(4-PIPERIDINYL)-1 1 H-BENZOFS.6iCYCLO- HEPTA(1 .2-b)PYRIDINE

Hydrolyze the title compound of Preparative Example 34A by dissolving in 50% aqueous sulfuric acid (v/v) and heating to 900 to 1000C for 16 h. The cooled acidic mixture was neutralized with 25% sodium hydroxide solution (w/v). The resulting mixture was extracted with ethyl acetate and the ethyl acetate extract was dried with sodium sulfate.

Filtration and evaporation of the ethyl acetate afforded the title compound(MH+ 311).

PREPARATIVE EXAMPLE 35
8-CHLORO-9-ETHYL-11-(4-PIPERIDINYL)-11H-BENZO [5.6]CYCLOHEPTA[1 .2-b]PYRIDINE

Hydrolyze the title compound of Preparative Example 34B following the procedure described in Preparative Example 34C to provide the title compound. 9Decomposes between 205.7-215.40C, heating 2-3 C per minute.

PREPARATIVE EXAMPLE 36
A. 8-CH LORO-11 -(1 -ETHOXYCARBONYL-4-PI PERIDINYL)- 11 H-BENZOtS.6]CYCLOH EPTAll .2-blPYRIDINE-1 -OXIDE

The title compound from Preparative Example 34A above (20.23 grams, 52.84 mmoles) was dissolved in dichloromethane (250 mL). 3
Chloroperoxybenzoic acid (1.25 equivalents) was added in one portion and this solution was stirred for 45

minutes. Sodium bisulfite solution (20% w/v) was added and the biphasic mixture rapidly stirred for 30 minutes. The layers were separated and the organic layer was washed with saturated sodium carbonate solution and dried with sodium sulfate.

Filtration and evaporation afforded the title compound (21g, 99%, mp 78.6-89.4 C, MH+ 399).

B. 4.8-DICHLORO-1 1-(1-ETHOXYCARBONYL-4-PIPERIDIN-YL)-11 H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE (A) and 2 .8-DICHLORO-l 1 -(1 - ETHOXYCARBONYL-4-PI PERIDI N- YL)-l 1 H-BENZOIS .6]CYCLOHEPTAt1 .2-B]PYRI DINE (B)

The title compound from Preparative Example 36A (21 grams, 53 mmoles) above was dissolved in anhydrous dichloroethane (250 mL) and the solution cooled to OOC. POCI3 (49.4 grams, 0.322 mole) was added dropwise to the dichloroethane solution over 15 minutes. After the POCI3 was added the reaction mixture was warmed to 45 - 500C and stirred for 18h. Additional POCI3 (8.2 grams) was added and the mixture heated to reflux for 9h. The mixture was cooled and added to an ice cooled, stirred solution of sodium hydroxide (15% w/v). The resulting biphasic mixture was stirred rapidly for 18h. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water followed by brine and dried (sodium sulfate).

The mixture was filtered and evaporated, and the residue chromatographed on silica gel using a gradient of 25% ethyl acetate in hexane to 45% ethyl acetate in hexane as eluent. The title compound A was obtained as a yellow solid (5.98 g M+ 417), and title compound B was obtained as a yellow solid (1.0 g, mp 84.4-90.60C).

C. 4.8-DICHLORO-11 -(4-PIPERIDINYL)-11 H-BENZOFS.61- CYCLOHEPTAT1 .2-blPYRIDINE

The title compound A from Preparative Example 36B was hydrolyzed under the conditions described in Preparative Example 34C to give the title compound (M+ 345).

PREPARATIVE EXAMPLE 37
A. 4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2 biPYRIDI N-il -YLI DENE)- 1 - (ETHOXYCARBONYL)-PI PERIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K.

By substituting in Preparative Example 2, 8-chloro-1 1 H-benzo[5,6]- cyclohepta[1,2-b]pyridin-11-one for 9-fluoro-5,6-dihydro-11H-benzo[5,6] cyclohepta[1 ,2-b]pyridin-1 1-one and employing basically the same methods as steps D through F of Preparative Example 2, one obtains the title compound (mp 154.7 - 155.50C).

B. 8-CHLORO-11-(4-PIPERIDINYL)-BENZO[5,6]CYCLO HEPTAtl .2-bPYRIDINE

Hydrolyze the title compound of Preparative Example 37A following the procedure described in Preparative Example 334C (mp 168.5 171 .20C, decomposition).

PREPARATIVE EXAMPLE 38
8-CHLORO-11-(1-PIPERAZINYL)-11H-BENZO[5,6]CYCLO HEPTA[1,2b]PYRIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguiy, A.K.

By substituting in Preparative Example 7A, 8-chloro-1 1 H-benzo[5,6]cyclo- hepta[1,2-b]pyridin-11-one

(11.53g) (47.71mmoles) for 8-chloro-5,6dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one and employing basically the same methods as steps A through C of Preparative Example 7, one obtains 11.539 (36%) of the title compound (MH+ 312).

PREPARATIVE EXAMPLE 39
A. ETHYL aa-DIMETHYL-3-PYRIDYLACETIC ACID N-OXIDE

By substituting in Preparative Example 8A, ethyl a,a-dimethyl-3pyridylacetic acid (4.0g, 20.7mmoles) for ethyl 3-pyridylacetic acid and using the same method as described in Preparative Example 8A, one obtains the title compound (3.29, 74%, MH+ 210).

B. a.a-DIMETHYL-3-PYRIDYLACETIC ACID N-OXIDE

By substituting in Preparative Example 8B, ethyl a,a-dimethyl-3pyridylacetic acid N-oxide (0.142g, 0.68mmoles) (Preparative Example 39A) for ethyl 3-pyridylacetic acid N-oxide and using the same method as described in Preparative Example 8B, one obtains the title compound.

PREPARATIVE EXAMPLE 40
4-BROMO-8-CHLORO-11-(1-PIPERAZINYL)-6.11-DIHYDRO-5H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

By substituting in Preparative Example 7A, 4-bromo-8-chloro-11-(1- piperazinyl)-5,6-dihydro-11H-benzo [5,6]cyclohepta[1,2-b]pyridin-11-one (1.5g, 4.65mmoles) (Preparative Example 20A) for 8-chloro-5,6-dihydro11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one and using the same methods as described in steps A through C of Preparative Example 7, one obtains the title compound (1.319, 72%, MH+ 392).

PREPARATIVE EXAMPLE 41
4,8-DICHLORO-11-(1-PIPERAZINYL)-6,11-DIHYDRO-5H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE

By substituting in Preparative Example 7A 4,8-Dichloro-5,6dihydro-11H-benzo[5,6]cycloheptal[1,2-b] pyridin-11-one (6.64g, 28.37mmoles) (Preparative Example 5B) for 8-ch loro-5,6-dihydro-l 1H- benzo[5,6] cyclohepta [1,2-b]pyridin-11-one and using the same methods as described in steps A through C of Preparative Example 7, one obtains the title compound (2.599, 26%, MH+ 348).

PREPARATIVE EXAMPLE 42
ETHYL 4-[4-[(1 H-B ENZOTRIAZOL- 1 -YL)OXYJ-8-CH LORO-5 .6-
DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]1-PIPERIDINE CARBOXYLATE

To a solution of the 4,8-dichloro compound from Preparative
Example 27 (1.5 grams) in dry dimethylformamide (20 mL) was added 1hydroxybenzotriazole (1.5 grams). After stirring for 14 days at 250C, sodium hydride (0.84 grams, 60% in mineral oil) was added and after an additional 24 hours, the mixture was poured into water. Filtration provided the title compound (Yield: 1.7 grams, 89%, mp = 181.5 - 183.9 OC, MH+ 516).

PREPARATIVE EXAMPLE 43
ETHYL 4-t4-HYDROXY-8-CHLORO-5 .6-DI HYDRO-1 1 H-
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE
CARBOXYLATE

To a solution of the title compound from Preparative Example 42 (0.15 grams) and glacial acetic acid (5 mL) was added zinc dust (0.2 grams). After stirring at 250C for 1 hour, the mixture was filtered through celite and the filtrate concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo to give the title compound (Yield: 0.11 grams, 95%, MH+

399).

PREPARATIVE EXAMPLE 44
ETHYL 4-[3-BROMO-4-HYDROXY-8-CHLORO-5.6-DIHYDRO-I 1 H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE
CARBOXYLATE

To a solution of the title compound from Preparative Example 43 (1.3 grams) and glacial acetic acid (5 mL) was added a 0.7 M bromineacetic acid solution (4 mL) at 250C under N2. The solution was poured into 200 mL of water and the resulting solid was filtered, then washed with water. The solid was dried under vacuum overnight to provide the title compound (Yield: 1.2 grams, 81%, MH+ 477).

PREPARATIVE EXAMPLE 45
ETHYL 4-[3-BROMO-4.8-DICHLORO-5.6-DIHYDRO-1 1 H-
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-PIPERIDINE
CARBOXYLATE

A mixture of the title compound from Preparative Example 44 (5.1 grams), phosphorous oxychloride (20 mL) and chloroform (40 mL) was stirred at reflux over night. The reaction mixture was made basic by the slow addition of 1 N aqueous sodium hydroxide, and the resultant mixture was diluted with dichloromethane. The mixture was shaken well and after separation of the phases, the organic phase was washed with 1 N aqueous sodium hydroxide. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to provide a solid which was mixed with methanol and filtered.

Concentration of the filtrate provided the title compound as a solid (Yield: 5.7 grams,MH+ 497).

PREPARATIVE EXAMPLE 46 3-BROMO-4. 8-DICHLORO-11-(4-PI PERIDYLIDENE)-6.11 -5H-
BENZO[5.6]CYCLOHEPTA[1 .2-bIPYRIDINE

A solution of the title compound from Preparative Example 45 (5.7 grams) dissolved in absolute ethanol (100 mL) and concentrated hydrochloric acid (200 mL) was stirred at reflux for 24 hours. The reaction mixture was cooled in an ice-water bath and was made basic by the addition of solid potassium hydroxide. Extraction with dichloromethane and concentration of the organic phase in vacuo afforded the title compound as a solid (1.7 grams, 35% yield, MH+ 425).

PREPARATIVE EXAMPLE 47
A 4-(8-CHLORO-3-NITRO-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTAI1 .2-bIPYRIDIN-II-YLI DENE)-
1 -PIPERIDINE-1-
CARBOXYLIC ACID ETHYL ESTER

Tetrabutyl ammonium nitrate(4.98g, 16.3 mmol) was dissolved in dichloromethane(20 mL) and trifluoroacetic anhydride(3.12g,14.9 mmol, 2.1 mL) was then added. The solution was cooled to 00C and then added (by cannulation) to a solution of 4-(8-chloro-5,6-dihydro-11 H-benzo[5,6]- cyclohepta[1,2-b] pyridin-1 1 -ylidene)-1 -piperidine-l -carboxylic aid ethyl ester (5.69g, 14.9 mmol) in methylene chloride (35 mL) also cooled to OOC. The reaction mixture was stirred at 0 C for 3h and then allowed to go to room temperature (250C) overnight. The reaction mixture was then extracted with saturated sodium bicarbonate (60 mL) dried over magnesium sulfate and concentrated to give a semi-solid material that was chromatographed on silica gel eluting first with 10% and then 20% ethyl acetate -hexane. Removal of the organic solvents gave the title compound in 44% yield as a light yellow solid. MP = 90.4-91.00C, MH+ 428.

B. 4-(8-CHLORO-3-AMINO-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOH EPTAII .2-bIPYRIDIN-I 1 -
YLIDENE)-1 -PIPERIDINE-1 -
CARBOXYLIC ACID ETHYL ESTER

The title compound from Preparative Example 47A (5.999, 14 mmol) was dissolved in 85% aqueous

ethanol. To this solution was added iron filings (7.01g, 125.57 mmol) and calcium chloride (0.69g, 6.29 mmol) and the reaction mixture was refluxed for 16h. The reaction mixture was filtered through a bed of celite while hot and the celite was washed with hot ethanol (700 mL). The ethanol solution was then decolorized with activated charcoal (2.4g) and then filtered through celite. Ethanol was then rotary eavaporated to give the title compound in 100% yield as an off-white solid. MP= 102.4-103.10C, MH + 398.

C. 4-(8-CHLORO-3-BROMO-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTAFl .2-biPYRIDIN-1 1 - YLIDENE)-1 -PIPERIDINE-1 -
CARBOXYLIC ACID ETHYL ESTER

The title compound from Preparative Example 47B (3.00g, 7.60 mmol) was dissolved in hydrobromic acid (48%, 30 mL). The reaction mixture was cooled to -50C (ice-ethylene glycol bath) and bromine(2 mL) was added dropwise. The reaction mixture was stirred at -50C for 15 minutes. Sodium nitrite (1.579, 22.8 mmol) dissolved in water (15 mL) was slowly added to the reaction mixture. The reaction mixture was then stirred for 45 minutes and then quenched with 40% NaOH to pH -10. The aqueous phase was then extracted with ethyl acetate(3x100mL).

Combined ethyl acetate fractions were dried over sodium sulfate and then concentrated to give the title compound in 83% yield as a light brown solid. Mp = 146-1480C, MH+ 463.

EXAMPLE 1
1 -(4-PYRIDYLACETYL)-4-(8-CH LORO-5.6-DI HYDRO- 11 H BENZO[5.6jCYCLOHEPTA(1 .2-b)PYRI DI N-1 1 -YLI DENE)PI PERI DINE

To a mixture of 528 mg (1.7 mmol) of 4-(8-chloro-5,6-dih yd ro-11H- benzo[5,6]cyclohepta[1,2-b]pyridin-11 -ylidene)piperidine (product from
Preparative Example 1, Step G), 274 mg (1.7 mmol) of 4-pyridylacetic acid hydrochloride, and 242 mg (1.8 mmol) of 1-hydroxybenzotriazole hydrate in 5 mL of dry methylene chloride at -15 C and under a nitrogen atmosphere was added dropwise 0.17 mL (1.5 mmol) of triethylamine followed by a solution of 363 mg (1.9 mmol) of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC) in 5 mL of dry methylene chloride. The reaction mixture was slowly allowed to warm to room temperature. After 4 hours the mixture was poured into water and extracted several times with methylene chloride. The combined organic portions were dried over MgS04, filtered, and concentrated in vacuo to give a product which was purified via flash chromatography (3% methanol saturated with ammonia in methylene chloride) 155 mg of 1-(4- pyridylacetyl)-4-(8-chloro-5,6-dihydro-1 1 H-benzo[5,6]cyclohepta[1 ,2- b]pyridin-11-ylidene) piperidine as a solid: mp 152 - 155 OC.

By essentially the same procedure as set forth in Example 1, but using the carboxylic acids set forth in column 1, of Table 2 below, in place of 4-pyridylacetic acid, one can obtain the compounds listed in column 2 of Table 2. The compounds listed in Table 2 refer to compounds of
Formula 500.00:

wherein R is the substituent in Column 2.

TABLE 2

EXAMPLE ¦ COLUMN 1 ¦ COLUMN 2 ¦ COMPOUND
JSN 9
OH
0S,0 OONO white powder
)cQi
4 oOH o white solid
N1 0 0113
013
OH or white crystals
5 uO Oo mp 2000C

or mop
6 mp 122-1250C
7 0' TLOH

TABLE 2 - continued

EXAMPLE COLUMN 1 COLUMN 2 COMPOUND
9 - - 0 glass
OH glass
10 ol white solid
NO2
NO2
11 Xo Lo white solid
OH
12 ; 05N glass
QI
OH
13 e OMeOMe white solid
OH
14 ot oe glass
OH mp
15 no NGi 176 -m1P78 C
OH H
16 - O < N glass
OH mp
17 01) mp 200 -2040C
NMe,

TABLE 2 - continued

EXAMPLE COLUMN 1 ~ COLUMN 2 ¦ COMPOUND
OH
18 N > eN glass
N
19 o glass
OH OH OH
20 OH OH 0NCIt yellow solid
OH 0 off
21 1) white solid
112
OH white solid
22 OH mp 2280C (dec)
N\ N\
s white solid
23 O < O O 205-207 C
OMe
O1)Me Of OMe white powder
OMe OMe
25 o ~ X white powder
0 0
26 N0 N0 glass
OH
27 OH N Oo N 9 lass

TABLE 2 continued

EXAMPLE ¦ COLUMN 1 ¦ COLUMN 2 ¦ COMPOUND
28 ta < glass
29 o & glass
30 OH ,H I ,H mp
O),N 211 -2150C
OH
31 ot <#s> NO2 o1)NO2 yellow solid
U OH
NQ NO2
OH
32 ¦ OI;NI white solid
33 OH N Od N white solid
HO N 10H HO N OH
34 OiH1;: 0%1 glass
0 0
Oi solid
35 OH solid mp
35 190- 1930C
OH 01
36 Otz 3 o%CHs solid

TABLE 2 - continued

EXAMPLE COLUMN 1 COLUMN 2 COMPOUND
OH
37 Ot CH3 OIf3 glass
a a
38 ow oS white solid
OH
39 oO o00 glass
40 OHN N mp
218-220"C
41 OH n n iight brown solid
mp=
OH OH 92.7 - 930C
MS M+ = 459
42 OH n ¦ 1 white solid
oe oX white
114.2- 1I5.80C
MS M+ = 506
43 , Br Br white solid
mp=
93.3- 94.60C
MS M+ = 506
44 or on 3 white solid
mp=
112 - 114.60C
MS M+ = 428
45 OH n n white solid
oNQ oJ NO2 mp =
94.3- 95.50C
MS M+ = 474

TABLE 2 - continued

EXAMPLE COLUMN 1 COLUMN 2 COMPOUND

46 o < NHCBZ OH NHCBZ white solid
0NHcBz 0 mp=
9 126.5 - 127.50C
<#s> OH OH OH MS M+ = 607
47 S9oCH3 oCH3 white solid
o 0 mp=
83.6- 85.00C
48 OH1 o white solid
mp=
CH3 CH3 82.7 - 83.80C
MS M+ = 456
49 nf OCH3 rnf OCH3 white solid
OH oW MS M+ = 534
o 0
49a OH I white solid
OH 0OH mp=
0
73.5 - 73.80C
288 O H O CH3 white solid
n e MH+ 452
I
Preparative Ex. 25
299 OH I off white solid
SUCH3 YCH3 MH+ 459
t: :
CH3 CH3
Preparative Ex. 26
300 O H O white solid
CH3 CH3 white solid
I\CH3 OINCH3 MH+ 459
Preparative Ex. 10

EXAMPLE 50
1-(2-THIOPHENEACETYL)-4-(8-CHLORO-5,6-DIHYDRO-11H BENZO[5.6]CYCLOHEPTA[1 .2-b] PYRIDIN-1 1 -YLIDENE)PIPERIDINE

To a solution of 1.0 gm (3.22 mmole) of 4-(8-chloro-5,6-dihydro 11 H-benzo[5,6]cyclohepta [1,2-b] pyridin-1 1-ylidene) piperidine and 0.29 mL of pyridine in 20 mL of dry methylene chloride at OOC and under an argon atmosphere was added dropwise 0.438 mL (3.55 mmol) of 2thiopheneacetyl chloride. After 30 minutes the mixture was washed with 1.0 N aqueous sodium hydroxide and then brine. The organic portion was dried over sodium sulfate, filtered and converted in vacuo to provide a residue which was purified via flash chromatography (3% methanol in methylene chloride) and treated with activated carbon to provide the title compound as a glass.

EXAMPLE 51
By essentially the same procedure as set forth in Example 50, but using the acid chlorides set forth in Column 1, in Table 3 below, in place of 2-thiopheneacetyl chloride, one can obtain the compounds listed in
Column 2 of Table 3. The compounds listed in Table 3 refer to compounds of Formula 500.00: :

wherein R is the substituent in Column 2
TABLE 3

EXAMPLE COLUMN 1 I COLUMN 2 COMPOUND
cm solid
O#Doi
a
013 013 solid

53 a 001013 mp
013 3 158-1600C
54 a o%ci glass
54 oAl;*l
55 O=% oi white powder
L/O
0 O01
013 + t mp
126 - 1280C
a 013 013 solid
57cm3 0013
)CH3 0a q3 Ov > 3 mp
137 - 1390C
a solid
58 O5; cH 4 ad mp
104 - 1060C
a white solid
59 0 013 0 013 155?f57CC

EXAMPLE 65
By essentially the same procedures as set forth in Example 50 above, or Example 4 of US 5,089,496, but using

in place of 4-(8-chloro-5,6-dihydro-l 1 H-benzo[5,6]cyclohepta[1 ,2-b]- pyridin-llylidene)piperidine, one can obtain the compound

as a white solid.

EXAMPLE 75
1 -(8-CHLORO-5.6-DI HYDRO- 11 H-BENZO[5.6]CYCLO-H EPTA[1 .2- b]PYRIDIN-11-YL-4-(4-PYRIDYLACETYL)-PIPERAZINE

To a mixture of 8.5 g (27.2 m mole) of 8-chloro-11-(1-piperazinyl)6.11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b]pyridine (Preparative
Example 7) in 256 mL of anhydrous dimethylformamide at room temperature and under an argon atmosphere was added 2.98 g (27.2 m
mole of 4-methylmorpholine, 7.81 g (27.2 m mole) of 1-(3-dimethyl
aminopropyl)-3-ethylcarbodiimide hydrochloride, 3.68 g (27.2 m mole) of
1 -hydroxybenzotriazole, and 3.72 g (27.2 m mole) pf 4-pyridylacetic acid.

The mixture was stirred at room temperature for 22 hours. The mixture
was poured into 3300 mL of methylene chloride and washed with 500 mL
of water. The aqueous layer was extracted with 500 mL of methylene
chloride. The combined organic portions were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a solution of 1.5% (10% ammonium hydroxide in methanol) in methylene chloride. The product was obtained as a white amorphous solid, M.S. (Mass Spec) M+ = 433.

By essentially the same procedures as set forth in Example 75 above but using the compounds set forth in Column 1, Table 4 below, in place of 4-pyridylacetic acid, one can obtain compounds of the formula

wherein R is as listed in Column 2 of Table 4.

TABLE 4

EX. I COLUMN 1 ¦ COLUMN 2 t CMPD
I white
76 I J o OH ¦ CN) ¦ amorphous

0 solid
0 00N Mass Spec
0
white
77 OH ~ CNg B amorphous
OS S solid
o42 Mass Spec
~ M+ = 512

TABLE 4 - continued

EX. COLUMN 1 CLUMN 2~ CMPD
I white
78 OHI (" amorphous
o I
Mass = Spec
0 M+=433
white
79 OH 1t rNA amorphous
N N q solid
Mass 0e Mass Spec
0 M+=508
NI
I
white
80 OH n CND amorphous
N N n solid
O N1 Mass Spec
0 M+=432
white
81 OH H1SH CNg amorphous
N CNJ N solid
0 CIr\ N Mass solid
H3 soNIs MM+S=S
O

EXAMPLE 82
8-CHLORO- 11 -[1 -(2-(4-PYRI DYL)ACETYL)-4-PI PERI DYLi-6. 11 DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]-PYRIDINE

Dissolve 0.1 g (0.32 m mole) of 8-chloro-l I-4-piperidyl]-6,1 1- dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine (from Example 233), 0.06 g (0.32 m mole) of 4-pyridylacetic acid, 0.092 g (0.48 m mole) of 1-(3dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.065 g (0.48 m mole) of N-hydroxy benzotriazole and 0.048 g (0.50 m mole) of N-methyl morpholine in 5 mL of dimethylformamide and stir at room temperature for 18 hours under nitrogen. Concentrate under vacuo and partition between 100 mL each of ethyl acetate and water. Dry the organic layer over sodium sulfate and concentrate under vacuo. The resulting residue is chromatographed on silica gel using 98% dichloro methane and 2% methanol, saturated with ammonia as the solvent, giving the product as a white waxy solid, mass spec M+ = 431.

EXAMPLE 82A
8-CHLORO-11-[1-(2-(PYRIDYL)ACETYL)-4-PIPERIDYL]-6.11 DIHYDRO-SH-BENZ015.61CYCLOHEPTAT1 .2-bIPYRIDINE

By essentially the same procedure as set forth in Example 82, but using 3-pyridylacetic acid instead of 4-pyridylacetic acid, the title compound is obtained as a white solid (M+ = 431, mp = 81.7-82 C).

EXAMPLE 83

8-CHLORO- 11 -(1 -(2-METHYLS ULFONYLOXY- 1 -PHENYLETHYL CHARBONYL)-4-PIPERIDYLIDENE]-6.11-DIHYDRO-5H-BENZO[5,6] CYCLOHEPTAFi .2-b]-PYRIDINE

Dissolve 0.40 g (0.9 m mole) of 8-chloro-11-[1-(2-hydroxy-1- phenylethylcarbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6] cyclohepta-[1,2-b]pyndine (Example 41 of Table 2) in 10 mL of pyridine and stir under nitrogen. Add 0.15 g (1.3 m mole) of methanesulfonyl chloride and stir for 20 hours. Concentrate under vacuo and triturate the residue with ether. Purify the resulting solid by silica gel chromatography using 2% methanol saturated with amonia, and 98% dichloromethane as the solvent. The product is obtained as a white solid, mp = 110.7-111.60
C.

EXAMPLE 84
8-CHLORO-11-[1-(2-ACETYLMERCAPTO-1-PHENYLETHYL CARBONYL)-4-PIPERIDYLIDENE]-6.11-DIHYDRO-5H-BENZO[5,6] CYCLOHEPTA[1 .2-b-PYRIDINE

Dissolve 0.3 g (0.56 m mole) of 8-chloro-11-[1-(2-methanesulfonyl- oxy-1 -phenylethylcarbonyl)-4-piperidylidene]-6, 11 -dihydro-SH-benzo [5,6]cyclohepta-[1,2-b]pyridine (Formula 5.6 of Example 83) in 5 mL of dimethylformamide and add 0.2 g (0.6 m mole) of cesium thioacetate (preparation described in Synthetic Communications, 13, 553, 1983). Stir the reaction at 800C for twenty hours then concentrate under vacuo.

Purify the residue by silica gel chromatography using 70% ethyl acetate and 30% hexane as the solvent. The product is obtained as a light brown
solid, mp = 92.7-93 C.

EXAMPLE 85
8-CHLORO-1 1 -(1(1 -(2.3-DI HYDRO-3-OXO-I .2-BENZOI SO-THIAZOL-S,S-DIOXIDE-2-YL)METHYLCARBONYL)-4-PIPERIDYL IDENE]-6.11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]-PYRIDINE

Dissolve 0.46g (1.7 m mole) of 8-chloro-1 1-[1-(2-hydroxyethyl- carbonyl)-4-piperidylidene]-6, 11 -dihydro-5H-benzo[5,6]cyclohepta [1,2,b]pyridine (Example 49a of Table 2) in 30 mL of dimethylformamide and stir at OOC under nitrogen. Add 0.55 g (2.1 m mole) of triphenyl phosphine and 0.36 g (2.1 m mole) of diethyl azodicarboxylate. Stir reaction mixture at 70 C for 3 days, then concentrate under vacuo. The residue was dissolved in 50 mL of 1 N hydrochloric acid and washed with 100 mL of ethyl acetate. The water layer was neutralized with 1 N sodium hydroxide and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under vacuo.

The residue was purified by silica gel chromatography using 90% ethyl acetate and 10% hexane as the solvent, giving the product as a white solid, mass spec. M+ = 534.

EXAMPLE 86 8-CHLORO-1 1-11 -(1 -(3-PYRIDYL)METHYLTHIOCARBONYL)-4-PIPERIDYLIDENE]-6.11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b] PYRIDINE

Dissolve 0.50 g (0.12 m mole) of 8-chloro-ll-[l-(l -(3-pyridyl)- methylcarbonyl)-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine (Example 2 of Table 2) and 0.5 g (0.12 m mole) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulifide (Lawesson's Reagent) in 15 mL of toluene and stirr for 18 hours at room temperature and 18 hours at 80 C, under nitrogen. Filter the reaction mixture and concentrate under vacuo. Disolve the residue in 50 mL of 1N hydrochloric acid and extract with 200 mL of dichloromethane. The water layer was neutralized with sodium carbonate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated under vacuo giving the product as a white solid, mp = 92-930C.

EXAMPLE 87
10.11 -DIHYDRO-5-[1 - (1 -(4-PYRIDYL)METHYLCARBONYL)-4- PIPERIDYLIDENE]-5H-DIBENZO[a.d] CYCLOHEPTENE

Dissolve 0.15 g (0.6m mole) of 10,11 -dihydro-5-(4-piperidylidene)
SH-dibenzo[a,d]cycloheptene, 0.096 g (0.55 m mole) of 4-pyridylacetic acid hydrochloride, 0.16 g (0.83 m mole) of 1-(3-dimethylaminopropyl)-3ethylcarbodiimide hydrochloride and 0.075 g (0.55 m mole) of N-hydroxy benzotriazole in 5 mL of dimethylformamide and stir at room temperature for 18 hours under nitrogen. Concentrate under vacuo and partition between 100 mL each of ethyl acetate and 10% aqueous sodium hydrogenphosphate. Dry the organic layer over magnesium sulfate and concentrate under vacuo. The resulting residue is chromatographed on silica gel using 98% dichloro methane and 2% methanol, saturated with ammonia as the solvent, giving the product as a white waxy solid, mp = 162.8-163.4 OC.

EXAMPLE 180 1 - 1 -(4-PYRIDINYLACETYL) -4-[3.8-DICHLORO-5.6-DIHYDRO- 11 H-BENZO[5,6] CYCLOHEPTA[1,2-b]PYRIDIN-11 -YLIDENE]
PIPERIDINE

Dissolve 0.18 g (0.51 mmole) of 3,8-dichloro 11-(1-acetyl-4piperidylidene)-6,11-dihydro-5H-benzo[5,6] cycohepta[1,2-b]pyridine, 0.0889 (0.51 mmole) 4-pyridylacetic acid, 0.1179 (0.61 mmole) of 1-(3dimethylaminopropyl)-3-ethylcarbodiim ide hydrochloride, 0.082g (0.61 mmole) N-hydoxybenzotriazole and 0.071g (0.71 mmole) N-methyl morpholine in 5 mL of dimethylformamide and stir for 18 hours under nitrogen. Concentrate under vacuo and partion between ethyl acetate and water. Dry organic layer over sodium sulfate and concentrate in vacuo. The resulting residue is chromatogaphed on silica gel using 95% dichloromethane and 5% methanol, saturated with ammonia as the solvent. The product is obtained as white solid, mp = 113-114 C.

EXAMPLE 181

By essentially the same procedure as set forth in Exampe 180, but using 8-bromo-11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo [5,6]cyclohepta[1,2-b]pyridine instead of 3,8-dichloro-1 1 -(1 -acetyl-4- piperidylidene)-6, 11 -dihydro-5H-benzo[5,6]-cyclohepta[1 ,2rb]pyridine, compound 5.48 was obtained as an off-white solid, mp= 94.3-94.7 C.

EXAMPLE 182

To a stirred solution of phenyl isocyanate (1.27 mmole) in 15 ml of anhydrous methylene chloride at room temperature and under an argon atmosphere was added dropwise over 20 minutes, a solution of 8-chloro 11 -(1 -piperazinyl)-6,11 -dihydro-SH-benzo[5,6]cyclohepta[1 ,2-b]pyridine (1.27 mmole) in 5 ml of anhydrous methylene chloride. The mixture was stirred at room temperature for 20 hours. The mixture was poured into 700 ml of methylene chloride and washed with 100 ml of saturated sodium bicarbonate. The organic portion was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using a solution of 1.0% (10% ammonium hydroxide in methanol) in methylene chloride. The product was obtained as a white amorphous solid, M.S. (Mass Spec) M+ = 433.

EXAMPLE 183

To a 5.0 ml reaction vial was added El-chloro-l l-(l-piperazinyl)- 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.0 mmole) and Nethoxycarbonyl-4-aminopyridine (0.99 mmole). The vial was capped and placed in an oil bath at 170 C and stirred for 5 hours. The residue was purified by silica gel chromatography using a solution of 3.0% (10% ammonium hydroxide in methanol) in methylene chloride. The product was obtained as a white amorphous solid, M.S. (Mass Spec) M+ = 434.

EXAMPLE 184
1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA [1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLACETYL)piperazine 1-N-OXIDE

The title compound from Preparative Example 11 D (0.5 grams) (1.5 mmoles) was reacted with 3-

pyridylacetic acid (0.208 grams) (1.5 mmoles) under the conditions described in Example 75 to give the title compound (Yield: 0.439 grams, 95%, MH+ 449).

EXAMPLE 185 1 -(8-CHLORO-6. 11 -DIHYDRO-5H-BENZO[5.6]CYCLOHEPTA [1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLACETYL 1-N-OXIDE)PIPERAZINE 1-N-OXIDE

The title compound from Preparative Example 11D (0.5 grams) (1.5 mmoles) was reacted with the title compound from Preparative Example 8 (0.232 grams) (1.5 mmoles) under the conditions described in Example 75 to give the title compound (Yield: 0.6454 grams, 92%, MH+ 465.2).

EXAMPLE 186
N-BENZYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTAT1 .2-blPYRIDIN-11 -YL)-1 -PIPERAZINECARBOXAMIDE

The title compound from Example 75 was reacted with benzyl isocyanate under the conditions described in Example 182 above to give the title compound (Yield: 79%, MH+ 447).

EXAMPLE 187
By essentially the same procedure as Example 183, with the exception that 3-ethoxycarbonylaminopyridine or 2-ethoxycarbonylamino pyridine (Preparative Example 12) is used instead of using 4-ethoxy carbonylaminopyridine, the compound

White amorphous White amorphous
solid, MH+ 434.3 solid, MH+ 434.3 was obtained, respectively.

EXAMPLE 188
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2 b]PYRIDIN-l 1 -YL)-N-METHYL-N-(3-PYRI DI NYL)- 1 -PIPERAZINE
CARBOXAMIDE

Compound 6.7 from Example 187 (10 grams) (23.1 mmoles) in DMSO (37.6 ml.) was added to a solution of powdered potassium hydroxide (2.62 grams) (23.1 mmoles) in DMSO (25 ml.) and the mixture was stirred at 250C for 3 minutes. Iodomethane (1.4518 ml.) (23.1 mmoles) was added and the mixture was stirred at 25 C for 15 minutes.

The mixture was poured into water and extracted with dichloromethane.

The latter was dried (magnesium sulphate), filtered and evaporated to dryness. The product was purified by chromatography on silica gel using 3-5%(10% concentrated ammonium hydroxide in methanol) dichloromethane as the eluant to give the title compound (Yield: 6.28 grams, 61%, MH+ 448).

EXAMPLES 189 - 218
By essentially the same procedures as set forth in Example 75 above but using the compounds set forth in Column 1, Table 5 below, in place of 4-pyridylacetic acid, one can obtain compounds of the formula

wherein R is as listed in Column 2 of Table 5.

TABLE 5

EX. ¦ COLUMN 1 ¦ COLUMN 2 ¦ CMPD
white
189 0 N amorphous
solid
HO N MH+ 475

0
N(CH3)2
(H3C)2N (5.62
.

I white
190 0 N amorphous
solid
HO CH3 N MH+ 460
CH3
I CH3
CH3
(5.li3)
HO he CH3 solid
MH+ 447
'"N CH3
0
(5.64)

TABLE 5 - continued

EX. COLUMN 1 COLUMN 2 ~ CM~PD
I white
- white
192 OH (" 9 (5.65) amorphous
CI .

o K o,I (5.65) solid
0
white
193 N /N amorphous
OH I (5.66) solid
I Q | (5.66) solid
N no MH+ 539
N 0
/f N
194 otNX t 9 (5.67) saomli drPh Us
t X ; MH+ 467 2

TABLE 5 - continued

EX. COLUMN 1 COLUMN 2 CMPD
OH C I white
H3 0?-G" solid
195 S CH3 no amorphous
MH+ 439
,CH3
0e
0 I white
196 < N amorphous
HO I ( ) (5.69) solid
NN N MH+ 433
0
\N
O I white

197 N amorphous
HO (5.70) solid
(5.70) solid
I $N- N 1+
"'N N0
TABLE 5 - continued

EX. <#s> COLUMN 1 7:: COLUMN 2 ¦ CMPD
O I white
198 HOtCH3 N amorphous
HO CH3
CH3 N J (5.71) solid
MH+ o4CH3 MH+ 461
"'N
CH3
CH3
tCH3
N
O 1s 72 white
199 OH) N amorphous
o)I FCH3 solid
0
5.72A = Isomer A
5.72B = Isomer B
O I white
200 N whi s
OH (5.73) solid
C S1 MH+ 467
A A
N

TABLE 5 - continued

EX. COLUMN 1 COLUMN 2 CMPD
I,CH, white
201 amorphous
201 OH ¦ N NI CH3 white
solid
0 NN MH+453
0
OH I white
202 N, amorphous
(5.75) soiid
N 0 t MH+ 525
0 N 0

Trifluroacetic Acid I white
203 deprotection of N amorphous
Compound 5.75 k J (5.76) solid
of Example 202 t MH+ 525
H
OH I white
204 OJn N (5.77) amorphous
< N OEt Q) (5.77) solid
o o <)
<#s> Ny0OEt
O

TABLE 5 - continued

EX. COLUMN 1 COLUMN 2 CMPD
c cH, (5.78) white
205 N 'N Oq~CH3 amorphous
MH+ MH+ 481
I white
t X ZCNICH3 ot;N C;3t j
0 ,ICH3 solid
J MH+ 453
OH3
0
OH H I white
207 o' I N1O Fh N
o I : > (5.80) amorphous
solid
(Ph=phenyl) NJ 7 SM0H0+d 505
(Ph=phenyl) O H
0
OH H
208 J d,K o I(white
5.81
(5.81) solid
(tBu=t-butyl) 0 H
(tBu=t-butyl) MH+ 471
0Ny0OtBu
,N\ .OtBu
I
OH H I white
209 o t 3 (5 82) amorphous
Oo razz solid
MH+ 489

TABLE 5 - continued

EX. s COLUMN 1 COLUMN2 CMPD
OH H I white
210 0N'1 tN) (5.83) amorphous
wO H N H solid
LN) <
0OH
OH H I white
N
211 0 1OH N (5.84) amorphous
H solid
0N'OH MH+ 505
0
OH H OH I white
212 soNs (9 (5.85) amorphous
OH SOlid
h MH+ 505
n a
o II
(5.86) amorphous
H solid
tT'N ~Ph MH+595

0
OH H I white
214 NOtBu CN) H amorphous
<#s> 0 N solid
N J > ,N OtBu MH+ 561
ao

TABLE 5 - continued

EX. ¦ COLUMN 1 ¦ COLUMN 2 ¦ CMPD
OH I white
NH2 white
215 S~I/NH2 ( ) (5.88) amorphous
solid
I) MH+461
NH2 MH+ 461
I
N0IN CN) (5 89) sWohiiodrphouswhite
216 oH
216 OH N) (5689) solid
Ph t; ;NS MH+ 591
O MH+ 591
OH H I white
217 0NPh N) (5.90) amorphous
O NH H solid
O MH+ 503
o
218 a (3 (5.91)
0eN solid
3"i? MH+ 519
OOH

EXAMPLE 219-222
By essentially the same procedure as set forth in Example 1, but using the acids set forth in Column 1 of Table 6 below in place of 4pyridylacetic acid, the compounds listed in Column 2 of Table 6 are obtained. The compounds listed in Table 6 refer to compounds of
Formula 500.00:

wherein R is the substituent in Column 2.

TABLE 6

EX. COLUMN 1 COLUMN 2 CMPD
OH white
219 oS t (5.92) amorphous
N solid
gt MH+ 482
m.p. =
192-193 C
oH NO2 ll white
220 or N (5.93) amorphous
O > N NO2 solid
MH+ MH+ 502
0o1
282-285"C
.white
221 oH\W!5s94) amorphous

0 N\1 solid
MH+ 485
0
OH white
222 (5.95) amorphous
solid
J SoC MH+ 514

EXAMPLE 223
A. (+)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11K(R)-YL)-4-(3-PYRIDINYLACETYL)PIPERAZINE

The title R(+) diastereoisomer from Preparative Example 19 was reacted with 3-pyridylacetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 88%, MH+ 433).

B. (-)-1-(8-CHLORO-5 .6-DIHYDRO-11 H-BENZOl5 .6lCYCLO-
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-(3-PYRIDINYLACETYL)PIPERAZINE

The title S(-) diastereoisomer from Preparative Example 19 above was reacted with 3-pyridylacetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 96%, MH+ 433).

EXAMPLE 224
A. (+)-4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE
CARBOXYLATE

The title R(+) diastereoisomer from Preparative Example 19 was reacted with 3-ethoxycarbonylaminopyridine under the same conditions as described in Example 75 to give the title compound (Yield: 81%, MH+ 434).

B. (-)-4-(8-CHLORO-6. 11 -DI HYDRO-5H-BENZOt5 .6lCYCLO-
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE
CARBOXAMIDE

The title S(-) diastereoisomer from Preparative Example 19 was reacted with 3-ethoxycarbonylaminopyridine under the same conditions as described in Example 75 to give the title compound (Yield: 80%, MH+ 434).

EXAMPLE 225
A. (+)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)
ACETYL]PIPERAZINE

The title R(+) diastereoisomer from Preparative Example 19 above was reacted with 1-N-acetylpiperidinyl-3-acetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 52%, MH+481).

B. (-)-1-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-[(1-ACETYL-4-PIPERIDINYL) ACETYLIPIPERAZINE

The title S(-) diastereoisomer from Preparative Example 19 above was reacted with 1-N-acetylpiperidinyl-3-acetic acid under the same conditions as described in Example 75 to give the title compound (Yield: 53%, MH+ 481).

EXAMPLE 226

A. (+)-1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11(R)-YL)-4-[(1-ACETYL-4-PIPERIDINYL).

CARBONYLPI PERAZI NE

The title R(+) diastereoisomer from Preparative Example 19 was reacted with 1-N-acetylisonipecotic acid under the same conditions as described in Example 75 to give the title compound (Yield: 90%, MH+ 467).

B. (-)-1-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11(S)-YL)-4-[(1-ACETYL-4-PIPERIDINYL)
CARBONYL]PIPERAZINE

The title S(-) diastereoisomer from Preparative Example 19 was reacted with 1-N-acetylisonipecotic acid under the same conditions as described in Example 75 to give the title compound (Yield: 93%, MH+ 467).

EXAMPLE 227
4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2b]PYRIDIN-11-YLIDENE)-1-[(4-
PYRIDINYL)ACETYL]-PIPERIDINE N1
OXIDE

To a mixture of 0.933g(3 mmol) of 4-(8-chloro-5,6-dihydro-1 1 H- benzo-[5,6]cyclohepta(1 ,2-b]pyridin-1 1 -ylidene)-piperidine (product from
Preparative Example 1, step G), 0.46g(3 mmol) of 4-pyridyl acetic acid Noxide (prepared as described in Preparative Example 8) 1-hydroxybenzotriazole (0.409, 3 mmol) in 20 mL of DMF at - 40C and under nitrogen atmosphere was added N- methyl morpholine(1.65 mL, 15 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (DEC) an reaction stirred overnight at room temperature. The volatiles were stripped off and the resulting semi-solid was partitioned between water and ethyl acetate. The aqueous phase was washed twice with ethyl acetate. Combined ethyl acetate fractions were dried over
Na2SO4 and concentrated. The crude product was purified via flash chromatography on silica gel (first eluting with 3% and then 5% methanol saturated with ammonia in methylene chloride) to give the title compound as a light brown solid(0.2g mp=128-130 OC MH+446).

EXAMPLE 228
4-(8-CH LORO-5.6-DI HYDRO-I 1 H-BENZO-T5.61CYCLOH EPTAII .2 b]PYRI DIN-11 -YLIDENE)-1 -[(3-PYRIDINYL)ACETYU-PIPERIDINE N1
OXIDE

By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4pyridyl acetic acid N-oxidethe title compound was obtained as a white solid (mp = 120-1210C, MH+=466).

EXAMPLE 229 4-(8-CHLORO-5.6-DIHYDRO-1 1 H-BENZO-[5.6]CYCLOHEPTA[1 .2- b]PYRIDIN-11-YLIDENE!-1-[(3-PYRIDINYL)ACETYL]- PIPERIDINE N4
OXIDE

4-(8-chloro-5,6-dihydro-1 1 H-benzo-[5,6]cyclohepta[1 ,2-b]pyridin11 -ylidene)-1 -[(3-pyridinyl)acetyl]-piperidine (1.0g, 2.33mmol) was dissolved in dry methylene chloride(50mL) at -100C. 3-Chloroperbenzoic acid (80-85% purity 1.1g, 5.13 mmol) was added and the reaction stirred at that temperature for 95 minutes. The reaction mixture was washed with sodium bisulfite and then with 10% NaOH. The organic phase was dried over magnesium sulfate and then concentrated. Purification on silica gel eluting, first with 4%, 6% and then 10% methanol in methylene chloride gave rise to the title compound as a white solid (0.29, 0.77 mmol
MH+=446).

EXAMPLE 230

4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO-[5,6]CYCLOHEPTA[1,2b]PYBIDIN-11-YLIDENE)-1-[(4-PYRIDINYL)ACETYL]-PIPERIDINE N4
OXIDE

By essentially the same procedures as set forth in Example 229 above, but using 4-(8-chloro-5,6-dihydro-1 1 H-benzo-[5,6]cyclohepta[1 ,2- b]pyridin-11-ylidene)-1-[(4-pyridinyl)acetyl]-piperidine instead of 4-(8chloro-5,6-dihydro-11H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) 1-[(3-pyridinyl)àcetyl]-piperidine the title compound was obtained as an off-white solid (MH+=446).

EXAMPLE 231
A. 8-CHLORO-11-(1-ETHOXYCARBONYL-4-PIPERIDYL
IDENE)-6.11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE
N-OXIDE

8-chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H benzo[S,6]cycloheptafl,2-b]pyridine (5g, 13.06 mmol) was dissolved in methylene chloride at -100C. 3-Chlorobenzoic acid(4.9g, 15.67 mmmol) was then added and the reaction mixture stirred for 95 minutes. The reaction mixture was taken up in methylene chloride and extracted with sodium bisulfite, 10% sodium hydroxide. The crude reaction product was purified on silica gel eluting first with 1% and then with 2% methanol in methylene chloride to give the title compound (2.7g, MH+ 399).

B. 8-CHLORO-I1 -(4-PIPERIDYLIDENE)-6. II-DIHYDRO-SH-
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE N-OXIDE

By essentially the same procedures as set forth in Preparative
Example 1 step G, but using 8-chloro-1 1-(1-ethoxycarbonyl-4- piperidylidene)-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridine Noxide instead of 8-chloro-1 1 -(1 -ethoxycarbonyl-4-piperidylidene)-6,1 1 -dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained and used for the next reaction without further purification (MH+ 327).

C. 4-(8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL)ACETYL]
PIPERIDINE N1.N4 DIOXIDE

By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4pyridyl acetic acid N-oxide and 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine N-oxide instead of 8chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2b]pyridine, the title compound was obtained as a white solid (mp=105107 C, MH+=462).

EXAMPLE 232
4-(8-CHLORO-5.6-DIHYDRO-1 1 H-BENZO-T5.61CYCLOH EPTAI1 ,2- blPYRIDIN-11 -YLIDENE)-1 -I(4-PYRIDINYL)ACETYL1- PIPERIDINE N1.N4
DIOXIDE

By essentially the same procedure as set forth in Example 227, but using 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclo hepta[1 ,2-b]pyridine N-oxide instead of 8-chloro-11-(4-piperidylidene)-6,11 -dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound was obtained as a light brown solid(MH+=462).

EXAMPLE 233
A. 8-CHLORO-6. 11 -DIHYDRO-1 1 -(4-PIPERIDINYL)-5H- BENZO[5.6]CYCLOHEPTA[1 .2-b]PYRIDINE (Product A) and
6,11-DIHYDRO-11-(4-PIPERIDINEYL)-5H-BENZO[5,6] CYCLOHEPTA[1.2-b]PYRIDINE (Product B)

Product A Product B
To a solution 66.27g (0.21 mole) of4-(8-chloro-5,6-dihydro-1 1 H- benzo[5,6]cyclohepta(1 ,2-b]pyridin- 11 -ylidene)-piperidine (product from
Preparative Example 1 Example, step G), in THF (1 L) was added lithium aluminum hydride (24.32g, 0.64 mole) and the reaction mixture was heated to reflux overnight. The reaction mixture was then cooled to room temperature and - 3L of diethyl ether is added followed by dropwise addition of saturated sodium sulfate until a white gray precipitate forms.

Magnesium sulfate was then added to the separated organic layer and stirred for 30 minutes. All the volatiles were then removed and the resulting crude mixture was chromatographed on a silica gel column eluting with 10% methanol saturated with ammonia in methylene chloride.

The material obtained contained both the desired compound and the deschloro compound. Separation on HPLC using reverse phase column and eluting with 40% methanol-water afforded the desired compounds as white solids (Product A's mp = 95.2-96.10C, Product B's mp = 145.1 1 45.7 C).

B. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO
HEPTA[1,2-b]PYRIDIN-11 -YL)-1 (3-PYRIDINYL)ACETYL]- PIPERIDINE N1 OXIDE

By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid N-oxide (Preparative Example 9) instead of 4pyridyl acetic acid N-oxide and 8-chloro-6,11-dihydro-11-(4-piperidinyl)- SH-benzo[5,6]cyclohepta[l ,2-b]pyridine (product from Example 233A) instead of 4-(8-chloro-5,6-dihydro-1 1 H-benzo-[5,6]cyclohepta(1 ,2- b]pyridin-11-ylidene)-piperidine, the title compound was obtained as a white solid (mp=117.118 C, MH+=414).

EXAMPLE 234
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA(1,2b]PYRIDIN-11-YL)-1-[(4-PYRIDINYL) ACETYL]- PIPERIDINE N1 OXIDE

By essentially the same procedure as set forth in Example 227, but
using 8-chloro-6,11-dihydro-11-(4-piperidinyl)-5H-benzo[5,6]cyclohepta [1 ,2-b]pyridine (product from Example 233A) instead of 4-(8-chloro-5,6- dihydro-11H-benzo-[5,6]cyclohepta(1,2-b]pyridin-11-ylidene)-piperidine
(product from Preparative Example 1, step G), the title compound was obtained as a white solid (mp=125-1260C, MH+=414).

EXAMPLE 235
A. ETHYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO [5,6]CYCLOHEPTA(1,2-b]PYRIDIN-11-YL)-1-PIPERIDINE
CARBOXYLATE

8-Chloro-6, 11 -dihydro-1 1 -(4-piperidinyl)-5H-benzo[5,6]cyclohepta- [1,2-b]pyridine (product from Example 233A) (4.18g, 13mmol) was dissolved in toluene (175mL). Ethyl chloroformate(11.6g,110 mmol, 10.2 mL) was then added and the reaction mixture was heated to ~120 C overnight. All volatiles were stripped off and the crude product was purified on silica gel column eluting with 50% ethyl acetate-hexanes to give the title compound as a white solid(MH+ 385).

B. ETHYL 4-(8-CHLORO-6.11 -DIHYDRO-5H-BENZO [5,6]CYCLOHEPTA(1,2-b]PYRIDIN-11-YL)-1-PIPERIDINECARBOXYLATE N OXIDE

By essentially the same procedure as set forth in Example 231, but using ethyl 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta(1,2 b]pyridin-1 1 -yl)-l -piperidineca rboxylate (product from Example 235A) instead of 8-chloro-11-(1 -ethoxycarbonyl-4-piperidylidene)-6, 11 -dihydro- 5H-benzo[5,6]cyclohepta[1,2-b] pyridine. the title compound was obtained as a white solid (mp= 81.7-82.50C, MH+=400).

C. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2
biPYRIDIN-1 1-YL)-1- PIPERIDINE N OXIDE

By essentially the same procedure as set forth in Preparative Example 1 step G, but using ethyl 4-(8-chloro-6,11-dihydro-5H-benzo- [5,6]cyclohepta[l ,2-b]pyridin-l 1 -yl)-1 - piperidinecarboxylate N1 oxide (product from Example 235B) instead of 8-chloro-11-(1-ethoxycarbonyl-4- piperidylidene)-6, 11 -dihydro-5H-benzo[5,6]cyclohepta[l ,2-b]pyridine, the title compound was obtained as a solid (MH+=329).

D. 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTA(1,2-b]PYRIDIN-11-YL)-1-[(3-PYRIDINYL)ACETYL]-PIPERIDINE N4 OXIDE

By essentially the same procedure as set forth in Example 227, but using 3-pyridyl acetic acid instead of 4-pyridyl acetic acid N-oxide and 4 (8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1piperidine N oxide (product from Example 235C) instead of 4-(8-chloro5,6-dihydro-11H-benzo-[5,6] cyclohepta[1,2-b]pyridin-11-ylidene)piperidine, the title compound was obtained as a white solid (mp=61.862.30C, MH+=448).

EXAMPLE 236
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2b]PYRIDIN-11-YL)-1-[(4-PYRIDINYL) ACETYL]- PIPERIDINE N4 OXIDE

By essentially the same procedure as set forth in Example 227, but using 4-pyridyl acetic acid instead of 4-pyridyl acetic acid N-oxide and 4 (8-chloro-6, 11 -dihydro-5H-benzo-[5,6]cyclohepta(1,2-b]pyridin-11 -yl)-1 piperidine N oxide (product from Example 235C) instead of 4-(8-chloro 5,6-dihydro- 11 H-benzo-[5 ,6] cyclohepta[l ,2-b]pyridin-ll -ylidene)piperidine, the title compound was obtained as a white solid (mp=116.7 117.6"C, MH+=448).

EXAMPLE 237
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA91,2 blPYRIDIN-11 -YL)-1 -[(3-PYflIDINYL)ACETYLi- PIPERIDINE Nl. N4
OXIDE

4-(8-Chloro-6, 1 1 -dihydro-5 H-benzo-[5,6]cyclohepta(1 ,2-b]pyridin- 11-yl)-1-[(3-pyridinyl)acethyl]-piperidine, from Example 82A, (0.5g, 1.2mmol) was disolved in methylene chloride at about -18 C. 3-Chloroperbenzoic acid (0.62g, 3.6 mmol) was added and the reaction stirred for 1.5 hours. The reaction mixture was extracted with 10% sodium bisulfite, 10% sodium hydroxide and then dried with magnesium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with 7% methanol saturated with ammonia in methylene chloride to give the title compound as a white solid(0.51g, 91% yield MH+ 464).

EXAMPLE 238
4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO-[5,6]CYCLOHEPTA(1,2b]PYRIDIN-11-YL)-1-[(4-PYRIDINYL) ACETYL]- PIPERIDINE N1. N4
OXIDE

By essentially the same procedure as set forth in Example 237, but using 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin11-yl)-1-[(4-pyridinyl)acetyl]-piperidine (product from Example 82) instead of 4-(8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl) 1-[(3-pyridinyl)acetyl]-piperidine, the title compound was obtained as a white solid (mp=85-85.6 C. MH+=464).

EXAMPLE 239
4-(8-CHLORO-3-METHOXY-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTAtl 2-b]PYRIDIN-11 -YLIDENE)-l -t(3-PYRIDINYL]ACETYL]-
PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 8-chloro-3-methoxy- 11 -(4-

piperidylidene)-6, 11 -dihydro-SH-benzo- [5,6]-cyclohepta[1 ,2-b]pyridine (Preparative Example 20) instead of 3,8dichloro-11-(1-acetyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6] cyclohepta[1 ,2-b]pyridine the title compound was obtained as a white solid (MH+ 460).

EXAMPLE 240
4-(8-CHLORO-3-HYDROXY-5.6-DIHYDRO-1 1 H-BENZOj'5.6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)-1-[(3-PYRIDINYL]-ACETYL] PIPERIDINE

4-(8-Chloro-3-methoxy-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2 b]pyridin-1 1 -ylidene)-1 -[(3-pyridinyl] acetyl]-piperidine (0.24g, 0.54 mmol) (Example 239) was dissolved in methylene chloride at OOC under nitrogen atmosphere. Bromine tribromide(0.9g, 3.6 mmol, 3.6 mL) was added and the reaction was run at room temperature for two days. The reaction mixture was concentrated and chromatographed on a silica gel column eluting with 3% methanol saturated with ammonia in methylene chloride to give an off white borate salt solid (0.14g, 61% yield, MH+ 446).

EXAMPLE 246
1-1(4-PYRIDINYLACETYL)-4-[3-BROMO8-CHLORO5-6-DIHYDRO11 H-BENZO[5.6]CYCLOHEPTAI1 .2-blPYRIDIN-1 1 YLIDENE]-PIPERIDINE

By essentialy the same procedure as set forth in Example 180 but using 4-(3-bromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta(1,2b]pyridin-11-ylidene)-piperidine instead of 4-(3,8-dichloro-5,6-dihydro 11 H-benzo-[5,6]cyclohepta(l ,2-b]pyridin-l 1 -ylidene)-piperidine, the title compound was obtained as a glassy solid (MH+ 508).

EXAMPLE 247
1-1(3-PYRIDINYLACETYL)-4-[3-BROMO8-CHLORO5-6-DIHYDRO11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE]-PIPERIDINE

By essentialy the same procedure as set forth in Example 180, but using 4-(3-bromo-8-ch loro-5,6-dihydro- 11 H-benzo[5,6]cyclohepta(1,2- b]pyridin-11-ylidene)-piperidine instead of 4-(3,8-dichloro-5,6-dihydro11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidine and 3pyridyl acetic acid instead of 4-pyridyl acetic acid, the title compound was obtained as a white solid (mp=92-930C MH+ 508).

EXAMPLE 248
4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA [1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLACETYL)-PIPERIDINE and
4-[2,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA [1,2-b]PYRIDIN-11-YLIDENE]-1-(4-PYRIDINYLACETYL)-PIPERIDINE

A solution of the title compound from Example 230 (1.7 grams) and phosphorous oxychloride (21 mL) dissolved in chloroform (12 mL) was stirred at reflux for 1 hour. Concentration in vacuo provided a residue which was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified by flash column chromatography (silica gel) using 2% methanol dichloromethane to afford the title 418-dichloro compound (0.34 grams, 20% yield, mp 84-91 OC, MH+ 464) and the title 2,8-dichloro compound (0.18 grams, 11% yield, mp 163.8-164.6 C, MH+ 464).

EXAMPLE 249
4-[4-[(1H-BENZOTRIAZOL-1-YL)OXY]-8-CHLORO-5,6-DIHYDRO11H-BENZO[5,6]CYCLOHEPTA[1,2-b] PYRIDIN-11-YLIDENE]-1-(4 PYR!DINYLACETYL)-PIPERIDINE

A mixture of the 4,8-dichloro compound from Example 248 (0.5 grams), 1-hydroxybenzotriazole hydrate (0.4 grams) and anhydrous dimethylformamide (20 mL) was stirred at 250C under N2 for 5 days. The

mixture was concentrated in vacuo, diluted with dichloromethane, and washed with 1 N aqueous sodium hydroxide. The organic phase was dried over anhydrous magnesium sulfate, concentrated in vacuo and purified by flash column chromatography (silica gel) using 3-5% methanol-dichloromethane to give the title compound (0.58 grams, 96%, mp 98.6-101.6 OC, MH+ 563).

EXAMPLE 250
4-[4,8-DICHLORO-5,6-DIHYDRO-11H-BENZO[5,6]CYCLO HEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLACETYL) PIPERIDINE

A mixture of the 4,8-dichloro product from Preparative Example 28 (1.91 grams), 3-pyridylacetic acid hydrochloride (2.1 grams), 1-(3dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.6 grams), 4methylmorpholine (1.4 mL) and anhydrous dimethylformamide (100 mL) was stirred at 25 C overnight. Concentration in vacuo provided a residue which was diluted with dichloromethane and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the title compound (2.2 grams, 87%, mp 59.8-63.5 C, MH+ 464).

EXAMPLE 251
4-[4-[(1 H-BENZOTRIAZOL-1 -YL)OXYl-8-CHLORO-5.6-DIHYDRO- 11 H-BENZO[5.6]CYCLOHEPTA[1 .2-b]PYRIDIN-1 1 -YLIDENE]-1-(3- PYRIDINYLACETYL)-PIPERIDINE

The 4,8-dichloro compound from Example 250 (0.8 grams) was added to a solution of 1-hydroxybenzotriazole hydrate (1.2 grams) and sodium hydride (0.14 grams, 60% in mineral oil) in anhydrous dimethylformamide (60 mL). The resulting solution was irradiated with a 200 W lamp while stirring at 250C for 60 hours. The solution was poured into 1 N aqueous sodium hydroxide while stirring and an additional 400 mL of water was added to the resulting mixture. Filtration provided a solid which was washed with water several times. The solid was dissolved in dichloromethane-acetone, dried over anhydrous magnesium sulfate, and concentrated in vacuo to proved the title compound (0.87 grams, 90%, mp = 120-122 C, MH+ 563).

EXAMPLE 252
4-[4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H-BENZO[5,6] CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3-PYRIDINYLACETYL) PIPERIDINE

To a solution of the title compound form Example 251 (0.8 grams) and glacial acetic acid (30 mL) was added zinc dust (0.4 grams). After stirring at 250C for 18 hour, the mixture was filtered through celite and the filtrate concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo to give the title compound (Yield 0.346 grams, 58%, MH+ 446).

EXAMPLE 253
4-[3-BROMO-4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3 PYRIDINYLACETYL)-PIPERIDINE

To a solution of the title compound from Example 252 (0.19 grams) and glacial acetic acid (4 mL) was added a 0.7 M bromine-acetic acid solution (0.7 mL) at 250C under N2. After 10 minutes, water was added and the resulting solid was filtered and washed with water several times and dried to give the title compound (0.18 grams, 71%, MH+ 526).

EXAMPLE 255
4-[8-CHLORO-4-(METHYLTHIO)-5,6-DIHYDRO-11H BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3 PYRIDINYLACETYL)-PIPERIDINE

A mixture of the title compound from Example 250 (0.26 grams), sodium methylthiolate (0.06 grams) and

an hydros dimethylformamide (10 mL) was stirred while being irradiated with a 200 W lamp for 1 hour.

After stirring an additional 12 hours at room temperature without irradiation, the mixture was concentrated in vacuo, diluted with dichloromethane, and washed with 1 N aqueous sodium hydroxide and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the title compound as a white foam (0.3 grams, 100%, MH+ 476).

EXAMPLE 256
4-18-CH LORO-4-(METHYLSULFI NYL)-5.6-DIHYDRO-11 H BENZO[5.6]CYCLOHEPTA[1 .2-bjPYRIDIN-1 1 -YLIDENE]-1 -(3-
PYRIDINYLACETYL)-PIPERIDINE

To the title compound from Example 255 (0.18 grams) dissolved in anhydrous tetrahydrofuran (10 mL) was added 30% aqueous hydrogen peroxide (3 mL) and the resulting solution was stirred for 12 hours at 730C. The solution was concentrated in vacuo, diluted with dichloromethane, and washed with water. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the title compound after preparative plate chromatography (silica gel) using 3% methanol-dichloromethane (0.04 grams, 26%, MH+ 492).

EXAMPLE 257
METHYL [[8-CHLORO-6,11-DIHYDRO-11-[1-[1-OXO-2-(3
PYRIDINYL)ETHYL]-4-PIPERIDINYLIDENE]-5H-BENZO[5,6]CYCLO HEPTA[1.2-b]PYRIDIN-4-YL]THIO]
ACETATE

A mixture of the title compound from Example 250 (0.26 grams), sodium hydride (0.08 grams, 60% in mineral oil), methyl thioglycolate (0.19 mL) and anhydrous dimethylformamide (15 mL) was stirred while being irradiated with a 200 W lamp for 16 hours. The mixture was diluted with methanol, concentrated in vacuo, diluted with dichloromethane and water, and washed with 1 N aqueous sodium hydroxide and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo and the residue purified by preparative plate chromatography (silica gel) using 3% methanol-dichloromethane to afford the title compound (0.05 grams, 15%, MH+ 534).

EXAMPLE 258
4-[8-CHLORO-5,6-DIHYDRO-4-(PHENYLMETHYLTHIO)-1H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1-(3
PYRIDINYLACETYL)-PIPERIDINE

A mixture of the title compound from Example 250 (0.25 grams), sodium hydride (0.11 grams, 60% in mineral oil), benzyl mercaptan (0.13 mL) and anhydrous dimethylformamide (15 mL) was stirred while being irradiated with a 200 W lamp for 10 days. Isolation and purification as in
Example 257 provided the title compound (0.02 grams, 8%, MH+ 552).

EXAMPLE 259
4-[8-CHLORO-5,6-DIHYDRO-4-[(2-METHYL-2H-TETRAZOL-5
YL)THIO]-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-1 (3-PYRIDINYLACETYL)-
PIPERIDINE

A mixture of the title compound from Example 250 (0.24 grams), 5mercapto-1-methyltetrazole sodium salt (0.6 grams) and anhydrous dimethylformamide (10 mL) was stirred while being irradiated with a 200
W lamp for 10 days. Isolation and purification as in Example 257 provided the title compound (0.2 grams, 68%, MH+ 544).

EXAMPLE 260
1.1-DIMETHYLETHYL (2-[[8-CHLORO-6,11-DIHYDRO-11-[1-[1
OXO-2-(3-PYRIDINYL)ETHYL]-4-PIPERIDINYLIDENE]-5H-BENZO[5,6] CYCLOH E PTA[1 .2-b]PYRI DI
N-4-YL]THI O]ETHYL] CARBAMATE

A mixture of the title compound from Preparative Example 32 (0.032 grams), 3-pyridylacetic acid hydrochloride (0.05 grams), 1-(3dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.03 grams), triethylamine (0.08 mL) and anhydrous dimethylformamide (4 mL) was stirred at 25 C for 48 hours. Concentration in vacuo provided a residue which was diluted with dichloromethane and washed with 1 N aqueous sodium hydroxide. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the title compound (0.02 grams, 50%, mp 59.8-63.5 C, MH+ 605).

EXAMPLE 261 4-(4.8-DICHLORO-5.6-DIHYDRO-1 1 H-BENZO[5.6iCYCLO-
HEPTA[1,2-b]PYRIDIN-11-YLIDENE)-N-(3-PYRIDYL)-1-PIPERIDINE
CARBOXAMIDE

A portion of the stock solution of 3-pyridylisocyanate (32 mL) prepared as described in Preparative Example 33 was added to the 4,8dichloro product from Preparative Example 28 (1.37 grams) and the mixture was stirred at 25"C for 4 days. The mixture was evaporated to dryness and the residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate and then water. The organic solution was dried over magnesium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography silica gel) using 2% methanol-dichloromethane as eluent to give the title compound (Yield 1.25 grams, 70%, MH+ 465).

EXAMPLE 262
4-14-1(1 H-BENZOTRIAZOL-1 -YL)OXY]-8-CHLORO-5.6-DIHYDRO- 11H-BENZO[5,6]CYCLOHEPTA
[1,2-b]PYRIDIN-11-YLIDENE]-N-(3
PYRIDYL)-1 -PIPERIDINECARBOXAMIDE

To a solution of the title compound from Example 261 (1.0 grams) in dry dimethylformamide (60 mL) was added 1-hydroxybenzotriazole (1.4 grams), sodium hydride (0.2 grams, 60% in mineral oil) and distilled water (0.5 mL). The solution was stirred at 250C under nitrogen while being irradiated with a 200 Watt lamp for 20 hours. The reaction mixture was concentrated in vacuo, diluted with dichloromethane and saturated aqueous sodium bicarbonate and after two hours, the organic phase was separated, dried over magnesium sulfate and concentrated. Purification by flash column chromatography (silica gel) using 3-5% methanoldichloromethane afforded the title compound (Yield 1.1 grams, 87%, MH+ 564).

EXAMPLE 263
4-(4-HYDROXY-8-CH LORO-5,6-D] HYDRO- 11 H-BENZOFS .6]- CYCLOHEPTAI1 .2-bIPYRIDIN-11-YLI
DENE1-N-(3-PYRIDYL-1 -
PIPERIDINECARBOXAMIDE

To a solution of the title compound form Example 262 (0.86 grams) and glacial acetic acid (20 mL) was added zinc dust (0.5 grams). After stirring at 250C for 1.5 hours, the mixture was filtered through celite and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) using 5-10% methanoldichloromethane saturated with ammonium hydroxide to give the title compound (Yield 0.47 grams, 69%, MH+448).

EXAMPLE 264
4-[3-BROMO-4-HYDROXY-8-CHLORO-5,6-DIHYDRO-11H
BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]-N-(3-PYRIDYL)
1 -PIPERIDINECARBOXAMIDE

To a solution of the title compound from Example 263 (0.34 grams) and glacial acetic acid (10 mL) was added a 0.7 M bromine-acetic acid solution (4 mL) at 25 C under N2. After 10 minutes, water was added and the resulting solid was filtered and washed with water several times and dried to give the title compound (Yield 0.31 grams, 67%, MH+ 527).

EXAMPLE 266
4-(8-CHLOflO-5H-BENZOts.6]CYCLOHEPTAjI .2-b]PYRIDIN-1 1 -
YL)-1 -(3-PYRIDINYLACETYL)-PIPERIDINE

The title compound from Preparative Example 34C (2.09, 6.4 mmole) was dissolved in anhydrous dimethylformamide (70 mL) and the solution was cooled with an ice bath for 30 minutes. 4-Methylmorpholine (3.3 g, 32 mmole), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.8 g, 9.7 mmole) and 1-hydroxybenzotriazole (0.879 6.4 mmole) were added to the cold solution. 3-Pyridylacetic acid (0.88 g, 6.4 mmole) was added and the cooling bath removed. Stir the mixture at room temperature for 18 hours. The reaction mixture was evaporated to dryness and the residue was diluted with water (50 mL). The aqueous mixture was extracted with ethyl acetate and the combined extracts dried (MgSO4), filtered and evaporated. The resulting residue was purifed by silica gel chromatography using a gradient of 97% dichloromethane/ 3% methanol saturated with ammonia to 93% dichlormethanet7% methanol saturated with ammonia as eluent to give the title compound (0.879 MH+ 430).

EXAMPLE 267
E. 4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2b] PYRIDIN-11-YL)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE

The title compound from Preparative Example 34C was treated with 3-pyridylisocyanate, similar to the procedure in Example 261, to afford the title compound (MH+ 431).

EXAMPLE 268
4-(8-CHLORO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11 YL)- 1 -[2-METHYL-2-(3-PYRI DI NYL)-1 -OXOPROPYLi-PI PERI DINE

The title compound from Preparative Example 34C was treated as described in Example 266, using cc,cx-dimethyl-3-pyridylacetic acid (described in Preparative Example 10B) in place of 3-pyridylacetic acid, to afford the title compound (M+ 458).

EXAMPLE 269
4-(8-CHLORO-5H-BENZO[5,6]CYCLOREPTA[1,2-b]PYRIDIN-11 YL)-1 -(4-PYRIDINYLACETYL)-PIPERIDINE

The title compound from Preparative Example 34C above was treated as descibed in Example 266, using 4-pyridylacetic acid in place of 3-pyridylacetic acid, to give the title compound (M+ 430).

EXAMPLE 270
4-(8-CHLORO-9-ETHYL-5H-BENZO[5,6]CYCLOHEPTA-[1,2b]PYRIDIN-11-YL)-1-(3-PYRIDINYLACETHYL)-PIPERIDINE

The title compound from Preparative Example 2A was treated as descibed in Example 266 to give the title compound (M+ = 458, mp = 67.2-69.8 C).

EXAMPLE 273
4-(4,8-DICHLORO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN11-YL)-1-(3-PYRIDINYLACETYL)-PIPERIDINE

The title compound from Preparative Example 36C was treated as descibed in Example 266 to give the title compound (mp 100.1 - 103.4 C).

EXAMPLE 274
4-(4,8-DICHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIBIDIN11-YL)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE

The title compound from Preparative Example 36C (0.75g, 2.17mmol) was treated with a pyridine solution

of 3-pyridylisocyanate (from Preparative Example 33). The reaction mixture was evaporated to dryness and the residue dissolved in dichloromethane. This solution was washed with saturated sodium bicarbonate solution and brine, dried (MgSO4), filtered and evaporated to give a dark syrup. The syrup was purified by silica gel chromatography using a gradient of 97% dichloromethane/3% methanol saturated with ammonia to 93% dichloromethane/70/0 methanol saturated with ammonia. The title compound was obtained as a yellow solid (0.139, 13%, M+ 465)
EXAMPLE 276
4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN11YLIDENE)-1-(3-PYRIDINYLACETYL)-PIPERIDINE

The title compound from Preparative Example 37B was treated as descibed in Example 266 to give the title compound (MH+ 428).

EXAMPLE 277
4-(8CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN11-YLIDENE)-N-(3-PYRIDINYL)-1-PIPERIDINECARBOXAMIDE

The title compound from Preparative Example 37B above was treated as descibed in Example 261 above to give the title compound (mp 95 -97.6"C).

EXAMPLE 278
4-(8-CHLORO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN11YLIDENE)-1-(2-METHYL-2-(3-PYRIDINYL)-1-OXO-PROPYL]
PIPERIDINE

The title compound from Preparative Example 37B was treated as descibed in Example 266 using or,a-dimethyl-3-pyridylacetic acid (described in Preparative Example 10B) in place of 3-pyridylacetic acid, to give the title compound (M+ 456).

EXAMPLE 279
4-(8-CHLORO-5,6-DIHYDRO-5-OXO-11H-BENZO[5,6]-CYCLO HEPTAI1,2-bIPYRI DIN-1IYLIDENE)-I -(3-PYRIDINYLACETYL)-
PIPERIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K.

The procedure described in Example 266 was followed using 8-chloro 6,11-dihydro-11-(4-plperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one to give the title compound (M+ 443).

EXAMPLE 280
4-(8-CHLORO-5,6-DIHYDRO-5-HYDROXY-11H-BENZO I5.61CYCLOHEPTAI1 ,2-bIPYRIDIN-11 YLIDENE)-1 -(3-PYRIDINYL ACETYL)-PIPERIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K.

The procedure described in Example 266 was followed using 8-chloro6,11-dihydro-5-hydroxy-11-(4-piperidinylidene)-5H-benzo[5,6]cyclo hepta[1 ,2-b]pyridine to give the title compound (MH+ 446).

EXAMPLE 281 4-(8-CHLORO-5,6-DI HYDRO-5-OXO-11 H-BENZOIS .61-CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYLACETYL)
PIPERIDINE

The procedure of Example 279 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound (MH+ 444).

EXAMPLE 282
4-(8-CHLORO-5,6-DIHYDRO-5-HYDROXY-11H-BENZO [5,6]CYCLOHEPTA[1 .2-b]PYRIDIN-1 1 YLIDENE)-1 -(4-PYRIDINYL ACETYL)-PIPERIDINE

The procedure of Example 280 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound (MH+ 446).

EXAMPLE 283
4-(8-CHLORO-5,6-DIHYDRO-6-OXO-11H-BENZO[5,6]
CYCLOHEPTAP[1,2-b]PYRIDIN-11YLIDENE)-1-(3-PYRIDINYLACETYL)
PIPERIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K.

The procedure described in Example 266 was followed using 8-chloro 6,11 -dihydro- 11 -(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1 ,2- b]pyridin-6-one to give the title compound (M+ 444).

EXAMPLE 284
4-(8-CHLORO-5.6-DIHYDRO-6-HYDROXY-1 1 H-BENZO jS.6]CYCLOHEPTA[1 .2-b]PYRIDIN-1 1 YLIDENE)-1 -(3-PYRIDINYL-
ACETYL)-PIPERIDINE

The preparation of the starting material for this reaction was described in The Journal of Organic Chemistry, 1990, 55, pp. 3341-3350 by Piwinski, J.J.; Wong, J.K.; Chan, T.-M.; Green, M.J.; and Ganguly, A.K.

The procedure described in Example 266 above was followed using 8chloro-6,11-dihydro-6-hydroxy-11-(4-piperidinylidene)-5H-benzo[5,6] cyclohepta[1 ,2-b]pyridine to give the title compound (MH+ 446).

EXAMPLE 285 4-(8-CHLORO-5.6-DIHYDRO-6-OXO-11 H-BENZ0[5.6]-
CYCLOHEPTA[1,2-b]PYRIDIN-11YLIDENE)-1-(4-PYRIDINYLACETYL)
PIPERIDINE

The procedure of Example 283 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound (M+ 444).

EXAMPLE 286
4-(8-CHLORO-5,6-DIHYDRO-6-HYDROXY-11H-BENZO [5,6]CYCLOHEPTA[1,2-b]PYRIDIN-
11YLIDENE)-1-(4-PYRIDINYL
ACETYL)-PIPERIDINE

The procedure of Example 284 was followed with the exception that 4-pyridylacetic acid was used in place of 3-pyridylacetic acid to give the title compound (MH+ 446).

EXAMPLES 287. 289 AND 290
By essentially the same procedure as in Example 1, but using either (R)-(+)- -methoxy- -(trifluromethyl)-phenylacetic acid (Example 290), (S)-(-)-o*-methoxy-a-(trifluromethyl)-phenylacetic acid (Example 287), or o:,a-dimethylphenylacetic acid (Example 289), the compounds of
Example 290, 287 and 289 were obtained. The structures for these compounds are in Table 7. Data for these compounds are: compound of

Example 290, white solid MH+ 527; compound of Example 287, white solid MH+ 527; and compound of Example 289, white solid M+ 457.

EXAMPLES 291. 292. 294. 313 AND 314
By essentially the same procedure as in Example 183, and using either 4-, 3-, or 2-ethoxycarbonylaminopyridine and either 4-(8-chloro-5,6dihydro-1 1 H-benzo[5,6]cyclohepta[1,2-b]pyridin-ll -ylidene)piperidine or 8-chloro-6,11-dihydro-11-(4-piperidinyl)-5H-benzo[5,6]cyclohepta[1,2b]pyridine (product of Example 233A), the compounds of Examples 291, 292, 294, 313 and 314 were obtained. The structures for the compounds of Examples 291, 292, and 294 are given in Table 7. The structures for the compounds of Examples 313 and 314 are given in Table 10.
Data are: the compound of Example 291 was a yellow solid (MH+ 431), the compound of Example 292 was an off white solid (MH+ 431), the compound of Example 294 was an off white solid (MH+ 431), the compound of Example 313 was a white solid (MH+ 433), and the compound of Example 314 was a white solid (MH+ 433).

EXAMPLE 301
1-1-(4-PYRIDINYLACETYL)-4-[3-METHYL-8-CHLORO-5,6
DI HYDRO- 11 H-BENZO[5 .6]CYCLOHEPTA(1 .2-b]PYRIDI N-I I -YLIDENE)-
PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-methyl-5,6-dihydro-1 1 -(4-piperidylidene)-1 1 H- benzo[5,6]cyclohepta[1 ,2-b]pyridine (from Preparative Example 3E) instead of 4-(3,8-dichloro-5,6-dihydro-1 1 -(4-piperidylidene)-1 1 H benzo[5 ,6]cyclohepta[l ,2-b]pyridine, the title compound was obtained as an off-white solid MH+ 444
EXAMPLE 303
1 - 1 - (3-PYRI DI NYLACETYL) -4t3-METHYL-8-CHLORO-5 .6-
DIHYDRO-1 1 H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-1 I-YLIDENE] -
PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-methyl-5,6-dihydro- 11 -(4-piperidylidene)-1 1 H- benzo[5 ,6]cyclohepta[l ,2-b]pyridine (from Preparative Example 3E) instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11Hbenzo[5,6]cyclohepta[1,2-b]pyridine, and 3-pyridylacetic acid instead of 4pyridylacetic acid, the title compound was obtained as white solid MH+ 444.

EXAMPLE 307
By essentially the same procedure as in Example 1, using the title compound from Preparative Example 37B, and 4-pyridylacetic acid the compound of Example 307, identified in Table 8, was obtained, MH+ 428.

EXAMPLE 309
1-1-(4-PYRIDINYLACETYL)-4-[2-METHYL-8-CHLORO-5,6
DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]
PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-2-methyl-5,6-dihydro-1 1 -(4-piperidylidene)-1 1 Hbenzo[5,6]cyclohepta[1,2-b]pyridine (from Preparative Example 3E) instead of 4-(3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H benzo[5,6]cyclohepta[1 ,2-b]pyridine, and 3-pyridylacetic acid instead of 4pyridylacetic acid, the title compound was obtained as white solid MH+ 444.

EXAMPLE 311 1-1-(4-PYRIDINYLACETYL)-4-F8.9 DICHLORO-5.6-DIHYDRO-1 1H-BENZO[5,6]CYCLOHEPTA[1 .2-b]PYRIDIN-1 1 -YLIDENE] - PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 4-(8,9-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6] cycloheptajl ,2-b]pyridine (from Preparative Example 1H) instead of 4 (3,8-dichloro-5,6-dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine, and 3-

pyridylacetic acid instead of 4-pyridylacetic acid, the title compound was obtained as white solid MH+ 464.

EXAMPLE 312
By essentially the same procedure as in Example 182, with the exception that 8-chloro-6,11-dihydro-11-(4-piperidinyl)-5H benzo[5,6]cyclohepta[1 ,2-b]pyridine is used instead of 8-chloro-1 1-(1- piperazinyl)-6, 11 -dihyd ro-5H-benzo[5,6]cyclohepta[1 ,2-b]pyridine, the compound of Example 312 was obtained as a white solid (MH+ 432). The structure for this compound is given in Table 10.

EXAMPLE 350 8-CHLORO-1 1 H-BENZO[5.S]CYCLOHEPTA[1 .2-b]PYRIDIN- 11 -YLIDENE)-4-(3-PYRIDINYLACETYL)PIPERAZINE

By substituting in Example 75, 0.4g (1.28mmoles) of 8-chloro-1 1 (1-piperazinyl)-11H-benzo[5,6] cyclohepta[1,2-b]pyridine (Preparative
Example 38) for 8-chloro- 11(1 -piperazinyl)-6, 11 -dihydro-SH-benzo[S,6]cyclohepta[1,2-b]pyridine and 0.1765g (1.28mmoles) of 3-pyridylacetic acid for 4-pyridylacetic acid and using the same method as described in
Example 75, one obtains the title compound (0.513g, 93%, MH+ 431).

EXAMPLE 351
1-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTA[1,2-b]PYRIDIN-11-YL)-4-(3-PYRIDINYLACETYL)PIPERAZINE

By substituting in Example 75, 3-bromo-8-chloro-11-(1 piperazinyl)-6, 11 -dihydro-5H-benzo [5,6jcyclohepta[1 ,2-b]pyridine (0.329, 0.8lmmoles) (Preparative Example 40) for 8-chloro-1 l-(1-piperazinyl)- 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and 3-pyridylacetic acid (0.117g, 0.86mmoles) for 4-pyridylacetic acid and using the method described in Example 50, one obtains the title compound (0.3942g, 95%,
MH+ 511).

EXAMPLES 352-353
By essentially the same procedures as set forth in Example 351, but using

in place of 3-pyridylacetic acid, one obtains compounds of the formulas

(Example 352) or (Example 353) respectively. The compound of Example 352 is a white amorphous solid, yield 65%, Mass Spec MH+ 555. The compound of Example 353 is a white amorphous solid, yield 59%, Mass Spec MH+ 539.

EXAMPLE 354
4-(3-BROMO 8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLO HEPTA[1,2-b]PYRIDINI-11-YL)-N-(3-PYRIDINYL)-1-PIPERAZINE CARBOXAMIDE

The title compound from Preparative Example 40 (0.37g, 0.94mmoles) was reacted with 3-ethoxycarbonylaminopyridine (Preparative Example 12) (0.123g, 0,94mmoles) under essentially the same conditions as described in Example 183, to give the title compound (0.3164g, 66%, MH+ 512).

EXAMPLE 355
1-(4,8-DICHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA ti .2-biPYRIDIN-I 1 -YL)A-(3-PYRIDYLACETYL PIPERAZINE

By substituting in Example 75, 4,8-chloro-11-(1 -piperazinyl)-6, 11 dihydro-5H-benzo[5,6]cyclohepta[I ,2-b] pyridine (0.3g, 0.86mmoles) (Preparative Example 41) for 8-chloro-1 1-(1-piperazinyl)-6,1 1-dihydro- SH-benzo[5,6]cyclohepta[1 ,2-b]pyridine and 3-pyridylacetic acid (0.1181 g, 0.86mmoles) for 4-pyridylacetic acid and using the method described in
Example 50 ,one obtains the title compound (0.3579, 88%, MH+ 467).

EXAMPLE 356
4-[3-BROMO-4.8-DICHLORO-5.6-DIHYDRO-1 1 H-BENZO[5.6] CYCLOHEPTAF1 .2-b]PYRIDIN-1 I -YLIDENE]-1 -(4-PYRI DINYLACETYL)-
PIPERIDINE

A mixture of the title compound from Preparative Example 46 (0.68 grams), 4-pyridylacetic acid hydrochloride (0.60 grams), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.65 grams), 4-methylmorpholine (0.6 mL) and anhydrous dimethylformamide (20 mL) was stirred at 250C for 48 hours. Concentration in vacuo provided a residue which was diluted with dichloromethane and washed with 1 N aqueous sodium hydroxide and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to provide a residue which was purified by flash column chromatography (silica gel) using 2-5% methanol-dichloromethane saturated with ammonium hydroxide to afford the title compound (0.06 grams, 7%, MH+ 544).

EXAMPLE 358
A. 4-(8-CHLORO-3-NITRO-5,6-DIHYDRO-11-(4 PIPERIDYLIDENE)-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINE.

Hydrolyze the title compound of Preparative Example 47A (10.09, mmol) by dissolving in conc. HCl (250mL) and heating to 1000C for 16h.

The cooled acidic mixture was neutralized with 1M NaOH (950 mL). The mixture was extracted with methylene chloride. The latter was dried over magnesium sulfate. Filtration and concentration afforded the title compound in 99% yield as a solid. MH+ 358.

B. 1-1-(4-PYRIDINYLACETYL) -4-13-BROMO-8-CHLORO-5.6-DIHYDRO-11H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE]
PIPERIDINE

By essentially the same procedure as set forth in Example 180, but using 4-(8-chloro-3-nitro-5,6-dihydro-1 I -(4-piperidylidene)-I 1 H benzo[5,6]cyclohepta[1 ,2-b]pyridine instead of 4-(3,8-dichloro-5,6dihydro-11-(4-piperidylidene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine.

the title compound was obtained as an off-white solid. Mp = 111.3112.20C, MH+ 475.

ASSAYS
1. In vitro enzyme assays: Inhibition of farnesyl protein transferase and geranylgeranyl protein transferase.

Both farnesyl protein transferase (FPT) and geranylgeranyl protein transferase (GGPT) I were partially purified from rat brain by ammonium sulfate fractionation followed by Q-Sepharose (Pharmacia, Inc.) anion exchange chromatography essentially as described by Yokoyama et al (Yokoyama, K., et al., (1991), A protein geranylgeranyltransferase from bovine brain: Implications for protein prenylation specificity, Proc. Natl.

Acad. Sci USA 88: 5302-5306, the disclosure of which is incorporated herein by reference thereto). Human farnesyl protein transferase was also expressed in E. coli, using cDNA clones encoding both the ol and ss subunits. The methods used were similar to those published (Omer, C. et al., (1993), Characterization of recombinant human farnesyl protein transferase: Cloning, expression, farnesyl diphosphate binding, and functional homology with yeast prenyl-protein transferases, Biochemistry 32:5167-5176). Human farnesyl protein transferase was partially-purified from the soluble protein fraction of E. coli as described above. The tricyclic farnesyl protein transferase inhibitors disclosed herein inhibited both human and rat enzyme with similar potencies. Two forms of val12-Ha-Ras protein were prepared as substrates for these enzymes, differing in their carboxy terminal sequence. One form terminated in cysteine-valine-leucine-serine (Ras-CVLS) the other in cystein-valine-leucine-leucine (Ras-CVLL). Ras-CVLS is a substrate for the farnesyl protein transferase while Ras-CVLL is a substrate for geranylgeranyl protein transferase I. The cDNAs encoding these proteins were constructed so that the

proteins contain an amino-terminal extension of 6 histidine residues. Both proteins were expressed in Escherichia coli and purified using metal chelate affinity chromatography. The radiolabelled isoprenyl pyrophosphate substrates, [3H]farnesyl pyrophosphate and [3H]geranylgeranyl pyrophosphate, were purchased from DuPont/New England Nuclear.

Several methods for measuring farnesyl protein transferase activity have been described (Reiss et al 1990, Cell 62: 81; Schaber et al 1990,
J. Biol. Chem. 265: 14701; Manne et al 1990, PNAS 87: 7541; and
Barbacid & Manne 1993, U.S. Patent No. 5,185,248). The activity was assayed by measuring the transfer of [3H]farnesyl from [3H]farnesyl pyrophosphate to Ras-CVLS using conditions similar to those described by Reiss et al. 1990 (Cell 62: 81) The reaction mixture contained 40 mM
Hepes, pH 7.5; 20 mM magnesium chloride; 5 mM dithiothreitol; 0.25 RM [3H]farnesyl pyrophosphate; 10 ul Q-Sepharose-purified farnesyl protein transferase; the indicated concentration of tricyclic compound or dimethylsulfoxide (DMSO) vehicle control (5% DMSO final); and 5 RM
Ras-CVLS in a total volume of 100 Al. The reaction was allowed to proceed for 30 minutes at room temperature and then stopped with 0.5 ml of 4% sodium dodecyl sulfate (SDS) followed by 0.5 ml of cold 30% trichloracetic acid (TCA). Samples were allowed to sit on ice for 45 minutes and precipitated Ras protein was then collected on GF/C filter paper mats using a Brandel cell harvester. Filter mats were washed once with 6% TCA, 2% SDS and radioactivity was measured in a Wallac 1204
Betaplate BS liquid scintillation counter. Percent inhibition was calculated relative to the DMSO vehicle control.

The geranylgeranyl protein transferase I assay was essentially identical to the farnesyl protein transferase assay described above, with two exceptions: [3H]geranylgeranylpyrophosphate replaced farnesyl pyrophosphate as the isoprenoid donor and Ras-CVLL was the protein acceptor. This is similar to the assay reported by Casey et al (Casey, P.J., et al., (1991), Enzymatic modification of proteins with a geranylgeranyl isoprenoid, Proc. Natl. Acad. Sci, USA 88: 8631-8635, the disclosure of which is incorporated herein by reference thereto).

2. Cell-Based Assay Transient expression of val12-Ha-Ras-CVLS and val12-Ha-Ras-CVLL in COS monkey kidney cells: Effect of farnesyl protein transferase inhibitors on Ras processing and on disordered cell growth induced by transforming Ras.

COS monkey kidney cells were transfected by electroporation with the plasm it pSV-SPORT (Gibco/BRL) containing a cDNA insert encoding either Ras-CVLS or Ras-CVLL, leading to transient overexpression of a
Ras substrate for either farnesyl protein transferase or geranylgeranyl protein transferase I, respectively (see above).

Following electroporation, cells were plated into 6-well tissue culture dishes containing 1.5 ml of Dulbecco's-modified Eagle's media (GIBCO, Inc.) supplemented with 10% fetal calf serum and the appropriate farnesyl protein transferase inhibitors. After 24 hours, media was removed and fresh media containing the appropriate drugs was re-added.

48 hours after electroporation cells were examined under the microscope to monitor disordered cell growth induced by transforming
Ras. Cells expressing transforming Ras become more rounded and
refractile and overgrow the monolayer, reminiscent of the transformed
phenotype. Cells were then photographed, washed twice with 1 ml of cold phosphate-buffered saline (PBS) and removed from the dish by scraping with a rubber policeman into 1 ml of a buffer containing 25 mM
Tris, pH 8.0; 1 mM ethylenediamine tetraacetic acid; 1 mM phenylmethylsulfonyl fluoride; 50 1M leupeptin; and 0.1 RM pepstatin.

Cells were lysed by homogenization and cell debris was removed by centrifugation at 2000 x g for 10 min.

Cellular protein was precipitated by addition of ice-cold trichloroacetic acid and redissolved in 100 ul of SDS-electrophoresis sample buffer. Samples (5-10 pl) were loaded onto 14% polyacrylamide minigels (Novex, Inc.) and electrophoresed until the tracking dye neared the bottom of the gel. Proteins resolved on the gels were electroblotted onto nitrocellulose membranes for immunodetection.

Membranes were blocked by incubation overnight at 40C in PBS containing 2.5% dried milk and 0.5% Tween-20 and then incubated with a
Ras-specific monoclonal antibody, Y13-259 (Furth, M.E., et al., (1982),
Monoclonal antibodies to the p21 products of the transforming gene of
Harvey murine sarcome virus and of the cellular ras gene family, J. Virol.

43: 294-304), in PBS containing 1% fetal calf serum for one hour at room temperature. After washing, membranes were incubated for one hour at room temperature with a 1:5000 dilution of secondary antibody, rabbit anti-rat IgG conjugated to horseradish peroxidase, in PBS containing 1% fetal calf serum. The presence of processed and unprocessed Ras-CVLS or Ras-CVLL was detected using a colorimetric peroxidase reagent (4-chloro-1-naphthol) as described by the manufacturer (Bio-Rad).

3. Cell Mat Assay:
Normal human HEPM fibroblasts were planted in 3.5 cm dishes at a density of 5 x 104 cells/dish in 2 ml growth medium, and incubated for 35d to achieve confluence. Medium was aspirated from each dish and the indicat - tumor cells, T24-BAG4 human bladder carcinoma cells expressing an activated H-ras gene, were planted on top of the fibroblast monolayer at a density of 2 x 103cells/dish in 2 ml growth medium, and allowed to attach overnight. Compound-induced colony inhibition was assayed by addition of serial dilutions of compound directly to the growth medium 24 h after tumor cell planting, and incubating cells for an additional 14 d to allow colony formation. Assays were terminated by rinsing monolayers twice with phosphate-buffered saline (PBS), fixing the monolayers with a 1 % glutaraldehyde solution in PBS, then visualizing tumor cells by staining with X-Gal (Price, J., et al., Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer, Proc.

Natl. Acad. Sci.84, 156-160(1987)). In the colony inhibition assay, compounds were evaluated on the basis of two ICs0 values: the concentration of drug required to prevent the increase in tumor cell number by 50% (tICso) and the concentration of drug required to reduce the density of cells comprising the cell mat by 50% (mICso). Both ICso values were obtained by determining the density of tumor cells and mat cells by visual inspection and enumeration of cells per colony and the number of colonies under the microscope. The therapeutic index of the compound was quantitatively expressed as the ratio of mICso/tIC50 with values greater than one indicative of tumor target specificity.

RESULTS OF ASSAYS - TABLES 7 TO 19
The compounds listed in Table 7 refer to compounds of Formula 500.00:

TABLE 7

EXAMPLE ¦ R ¦ FPT ICso (uM)
d
1 oi 0.01-10
a
IFN 0.01-10
3 OA 0.01-10
$0
88 iN 0.01-10
4 i Ft <
4 ICH3
7Ch3 0.01-10
CHS I
5 to 0.01-10
89rfCH, 0.01-10
0
6 o# <#s> ;) 0.01-10
7 OH 0.01-10
OH

TABLE 7 - continued

EXAMPLE R ~~ FPT IC50 (fly)
oWIoH 0.01-10
OH
90 et 0.01-10
S02NH2
91 eQ 0.01-10
NHSO2CH 3
92 is 0.01-10
SO2NHCH 3
.I9- 0.01-10
S02CH3
a
94 u SOCH3 0.01-10
socH3
9 I 0.01-10
0
95 51 0.01 -10
SO2
10 0.01-10
NO2
11 (o 0.01-10
12 O; ;s, 0.01-10

TABLE 7 - continued

EXAMPLE R ¦ FPT ICso (M)
0.01-10
96 0.01-10
97 out, 0.01-10
98 C CI 0.01-10
-N
99 eN 0.01-10
13.Xf e 0.01-10
0
100 olC 0.01-10
101 4 ¦ NH 0.01-10
Iph
102
0.01-10
103 olC 0.01-10
104 j4 OH 0.01-10

TABLE 7 - continued

EXAMPLE R FPT IC5o (us)
15 Np 0.01-10
6H
16 O < N 0.01-10
17 t 0.01-10
NMe2
52 Oi <#s> 0.01-10
18 iN 0.01-10
N
105 t NH2 0.01-10
NH2

19A e 0.01 -10
OH
20 0CH, 1-3 0.01-10
0.01-10
54
21 i NH2 0.01-10
NH2

TABLE 7 - continued

EXAMPLE n R ~¦ FPT ICso (AM)
L
55 4 0.01 -10
.

oV
22 i NXo 0.01-10
A
s
24 Of OMe
OH
OMe
25 XN 0.01-10
26 SL 0.01-10
108 Otk) 0.01-10
SMe
109 NHcH3
109 -N 0.01-10
27 0N 0.01-10
.

MINO
28 0.01-10

TABLE 7 - continued

EXAMPLE R FPTIC5o(uM)
56 oi ad3 0.01 -10
29 & 0.01 -10
H I
30 t' 0.01 -10
NO2
31 of OH 0.01-10
NO2
110 NMe2 0.01-10
111 O$L) 0.01-10
NHSO2CF3
32 N 0.01-10
33 OH 0.01 -10
" CH3 0.01-10
CH3 0.01-10
34 o 0.01 -10

TABLE 7 - continued

EXAMPLE ss R ¦ FPT IC50 (uM)
CHS
5 7 CH 3 0.01 - 1 0
35 Oe 0.01-10
N'N
113 cCH3 10-100
CH3
0
114 o$jN 10-100
36 cH CH3 10-100
0
37 of CH3 10-100
Nv
a
38 O 10-100 10-100
39 onto 1 10-100
10-100
115
0
58 O LasCH3 10-100

TABLE 7 - continued

EXAMPLE R FPT IC50 (CLM)
116
10-100
CH3
117h, 10-100
N 3
118 NH, 1 0-1 00
119 oOMe 10-100
119 I 10-100
OMe
120 OO4 //O 10-100
H
121 Si 0.01 10
40 o;t 10-100
INP
122 o)O 10-100
0
123 oX 10-100
0

TABLE 7 - continued

EXAM PLE I R FPT IC5o(M)
124 of cH3 10-100
e CH 3
125 o: b 10-100
HO
NO2
126 O#\ oX 0.01 -10
OH
127 oX OH 0.01-10
128 X,OH 0.01-10

129 -SH 10-100
0 \ NH
41 c 0.01 -10
~~ ~~ (5.4)
42 (5.4) 0.01 -10
(5.7)
Br
43 jmr 0.01-10
0 (5.8)
44 o'l (5.9) 0.01-10

TABLE 7 - continued

EXAMPLE R FPT IC50 (CLM)
45 0 N02 0.01-10
45 (5.1 1) 0.01-10
46 On 0.01-10
OH (5.12)
OH3
47 (5.13) 0.01-10
o (5.13)
48 43 0.01-10
CH3
(5.14
OcH3
0.01-10
o (5.15)
84 0.01-10
scocH3
(5.5)
83 0.01-10
OSO2CH3 (5.6)

19 5 (5.10) 0.01-10
0
851SL 0.01-10
0' '0 (5.16)

TABLE 7 - continued

l | ;
EXAMPLE R ¦ FPT ICso (IIM)
H
219 ' N
0
o
(5.92)
NO2
220 Oe 0.01-10
b 0.01-10
221 OOX 0.01-10
(5.94)
222 O > SC
N 0.01-10
o
227e N/
(5.102)

228 L MIN1
0 0.01-10
(5.103)
287 OM43 0.01-10
MeO cF3

TABLE 7 - continued

EXAMPLE R FPT ICso (uM)
N
288 O 0.01-10
289 0 0.01-10
290 43 0.01-10
Me0 F3
291 N/ N
I 0.01-10
H
292 N' 0.01-10
293 H 0.01-10
H
294 O; ref 0.01-10
NO2
295 ' 0.01-10

TABLE 7 - continued

EXAMPLE ¦ R I FPT ICso (uM)
296 owDi 0.01-10
o
N(CH3)2
297 o6 0.01-10
0
298 oS 0.01-10
MN
N
299 Ow 0.01-10
H3C CH3
300 0.01-10
; 300 ¦ H3C CHa

The compounds listed in Table 8 refer to compounds of Formula 505.00:

TABLE 8

FPT
EXAMPLE A B IC50
(uM)
74B Br9o a CH3 0.01-10
a
74C Cv Cl CH3 10-100
N
0
00H3
74A ,Cl CH3 10-100

0
130 CH3 10-100
Me
131 < > O 10-100
0
73 S a CH3 10-100
0
a
132 N CH3 10-100
0

TABLE 8 - continued

FPT
EXAMPLE A B ICso
(uM)
133cr
133 vCI CH3 10-100
0 cH
134 t
0
135 cm CI CH3 0.01-10
62 cm CH3 0.01-10
64 H3C > X9CI CH3 10-100
OCH
136 > C Hs 10- 100
66 %N# ;I\CI CH3 10-100
cH3
137 ¦ cii, CH3 10-100

TABLE 8 - continued

FPT
EXAMPLE A B ¦ FPT
(uM)
63 HSC9 CH3 100
0
139 H3cM!$cI CH3 10-100
140 9 CH3 10-100
71A Wi CH3 10-100
N
141 9 CH3 10-100
143 N9a CH3 10-100
143 CH3 10-100
OMe
71B mOMe CH3 10-100
CH3 10-100
144 CH3 10-100
N 1\CI
144a LIo 10-100
71C 6F < CI CH3 10-100

TABLE 8 - continued

<#s> FPT

EXAMPLE A B ICso
(uM)
yi$F oH3
145 > 100
1 46 X O 1 10-100
147 69 CH3 > 100
N
301 H30i$Oi JN 0.01-10
ci,
180 N 0.01-10
N
303 H30%i$Ci 0.01-10
303 j 0.01-10
(H3C)3(
304 0.01-10
305 (H3c),c JN 10-100
230 cm 0.01-10
0

TABLE 8 - continued

FPT
EXAMPLE A B IC50
(uM)
Cl N
307 m N'1 0 0.01-10
235 - N 0.01-10
N
OIH
309 H3C9 Cl 0.01-10
. ~
N
310 N' J3N 0.01-10
cl
311 1 mCl N I 0.01-10
ci
323
0.01-10
5.39 cr
N1 9 on 0.01-10
358 02N ~ ACl eN
tNW \ 0.01-10

TABLE 8 - continued

FPT
EXAMPLE ¦ A ¦ B ¦ IC50
(cam)
360 Br ACID O
Br ---'
N1 0.01-10
H3C CH3
361 Br /\Cl
Br N1
H30 OH3 0.01-10
362 \cl N
0.01-10

N Et
365 0.01-10
366 \N) 0.01-10
H
Ms
H
367 C t 0.01-10
N
H

Table 9 lists FPT IC50 results for additional compounds.

TABLE 9

EXAMPLE FPT IC50 EXAMPLE FPT IC50 EXAMPLE FPT IC50
(M) (M) (M)
229 0.01-10 231 10-100 232 0.01-10
(5.104) (5.106) (5.107)
236 0.01-10 237 10-100 238 10-100
5.111) (5.112) (5.113)
239 0.01-10 240 0.01-10 246 0.01-10
(5.114) (5.115) (5.121
247 0.01-10 248 0.01-10 248 0.01-10
(5.122) (5.124) (5.123)
249 0.01-10 250 0.01-10 256 0.01-10
5.125 (5.126) (5.132)
257 0.01-10 258 10-100 259 0.01-10
(5.133) (5.134) (5.135)
260 0.01-10 266 0.01-10 269 0.01-10
(5.136) (5.138) (5.140)
276 0.01-10 279 0.01-10 280 10-100
(5.145) (5.147) (5.148
281 0.01-10 282 0.01-10 283 0.01-10
(5.149) (5.150) (5.151)
284 0.01-10 285 0.01-10 286 0.01-10
(5.152) (5.153) (5.154)

The compounds listed in Table 10 refer to compounds of Formula 510.00:

TABLE 10

EXAMPLE 0 R 0 FPT IC50 (I1M)
149 N oo
= CHaq 3
150 t 10-100
OOH3
75 N) eN 0.01-10
(5. (5.17)
76 t) ':\)o 0.01-10
J NW
(5.18)
N
77 r) Br 0.01-10
(5.19)
78 ( ) i' < 0.01-10
(5.20)

79 tW 0.01-10
O
(5.21 (5.21)

TABLE 10 - continued

EXAMPLE R ~FPTIC50 (LM)
I
80 o.oi-10
81 X 3 0.01 -10
H SH
0 (5.23)
82 j.25) 0.01-10
(S .25)
312 is) 0.01-10
oAi'
H
313 4 0.01-10
L ; <#s> ;I
314 Di 0.01-10
H
234 C o 0.01-10

TABLE 10 - continued

EXAMPLE R FPT ICso (uM)
316 C I 0.01-10
H3C OH3
317 rI 10-100
OEt
0
318 ;{Ph 0.01-10
H
182 ,) 0.01-10
Ph
H
183 t) 0.01-10 t
0
H
a
321 gt 0.01-10

TABLE 10 - continued

EXAMPLE R I FPT IC50 (LM)
368 1
I CtD I > 100
> 100
H

Table 11 lists FPT IC50 results for additional compounds.

TABLE 11

EXAMPLE FPT IC50 EXAMPLE FPT IC50 EXAMPLE FPT IC50
(M) (M) (M)
187 0.01-10 187 0.01-10 188 0.01-10
(6.7) (6.8) (6.9)
189 0.10-10 190 0.01-10 191 0.01-10
(5.62) (5.63) (5.64
192 0.01-10 194 0.01-10 195 0.01-10
(5.65) (5.67) (5.68)
196 0.01-10 197 0.01-10 198 0.01-10
(5.69) (5.70) (5.71)
199 10-100 199 10-100 200 0.01-10
(5.72A) (5.72B) (5.73)
201 0.01-10 202 10-100 203 10-100
(5.74) (5.75) (5.76)
205 0.01-10 206 0.01-10 207 10-100
(5.78) (5.79) (5.80)
208 0.01-10 209 0.01-10 210 0.01-10
(5.81) (5.82) (5.83)
211 0.01-10 212 0.01-10 213 10-100
(5.84) (5.85) (5.86)
214 > 100 215 10-100 216 10-100
(5.87) (5.88) (5.89)

TABLE 11 - continued

EXAMPLE FPT IC50 EXAMPLE FPT IC50 EXAMPLE FPT IC50
(M) (M) (M)
217 0.01-10 218 0.01-10 233 0.01-10
(5.90) (5.91) (5.108)
251 0.01-10 # 261 0.01-10 351 0.01-10
(5.127) (6.12)
352 0.01-10 353 0.01-10 354 0.01-10
355 0.01-10 273 0.01-10 267 0.01-10
(5.143) (6.17)
356 0.01-10 264 > 100 262 0.01-10
(6.15) (6.13)
263 0.01-10 253 0.01-10 350 0.01-10
(6.14) ¦ (5.129)
252 0.01-10 182 0.01-10 268 0.01-10
(5.128) (6.4) (5.139)
277 0.01-10 --- --- --
(620)

The compounds listed in Table 12 refer to compounds of Formula 525.00: :

TABLE 12

FPT
EXAMPLE A B ICso
(uM)
N
184(5.60) 0.01
10 10
0
185(5.61) - N 0.01

10
N
223(5.96) t - JU3 o1oo1
223 (5 97} X cl t 10
N
224(6.10) - 0.01
N' H 10
224(6.11) IIN'5:'\ 0f01
H 0
225(5.98) IACH3 0.01
N 10

TABLE 12 - continued

FPT
EXAMPLE A B IC50
(uM)
225 (5.99) X CPN)ICH, 0.01
N: mi 10
ACI
226 (5.100) QNYJ 0.01
10 CH3 10
------- MA: ci 10
226 (5 101) XCI 0.01
351 yN'H'$0 Mi Of01
351 10
354 a X CI H O 0.01
H I
H 10

The compounds listed in Table 13 refer to compounds of Formula 515.00: :

TABLE 13

EXAMPLE R FPT IC50)
K] 10-100
151) 10-100
0
152 10-100
b, 10-100
H
153 CN) 10-100
N
.dCH3
87 t 0.01-10
IN
OW (5.24)

Additional FPT IC50 results were: (1) Example 180, compound 5.47, 0.01-10 uM; (2) Example 181, compound 5.48, 0.01-10 uM; (3)
Example 182, compound 6.4, 0.01-10 M; and (4) Example 183, compound 6.5, 0.01-10 M.

TABLE 14
COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

EXAMPLE ENZYME INHIBITION ENZYME INHIBITION
FPT IC50 M GGPT IC50 M
1 0.01-10 > 46
2 0.01-10 > 46
3 0.01-10 > 39
5 0.01-10 > 46
7 0.01-10 > 45
8 0.01-10 42
181 ~ 0.01-10 > 42

TABLE 15
ACTIVITY IN COS CELLS

Example Inhibition of Ras Example Inhibition of Ras
Processing Processing
IC50 (M) IC50 (M)
1 0.01-10 --- --
82 0.01-10 156 (5.46) 0.01-10
75 0.01-10 2 0.01-10
45 0.01-10
78 0.01-10 42 0.01-10
19 0.01-10 89 0.01-10
83 0.01-10 5 0.01-10
77 0.01-10 43 0.01-10
6 0.01-10 49 10-100
47 10-100 44 10-100
87 10-100 46 10-100
85 10-100 84 10-100
3 10-100 76 10-100
154 (5.28) 10-100 48 10-100
5 10-100 88 10-100
53 10-100 181(5.48) 0.01-10

In Table 15, the numbers in parenthesis in the Example column refer to the formula number for the compound used in the indicated example. Also, the compound of Example 157 is:

TABLE 16
INHIBITION OF TUMOR CELL GROWTH
MAT ASSAY

Example Tumor Normal Example Tumor Normal
IC50 IC50 IC50 ICso
M) (uM) (M) (M)
75 2.5 > 50.0 ---- ---- ---
1 3.1 25.0 82 3.1 40.0
5 6.3 > 50.0 89 6.3 > 25.0
127 6.3 > 50.0 45 6.3 > 50.0
88 8.0 > 50.0 6 12.5 50.0
49 12.5 > 50.0 47 12.5 > 50.0
48 12.5 25.0 79 12.5 > 50.0
158 (5.36) 12.5 18.0 2 25.0 > 50.0
10 25.0 > 50.0 128 25.0 > 50.0
44 25.0 25.0 164 (5.30) 25.0 > 50.0
43 25.0 50.0 165 (5.34) 25.0 50.0
53 25.0 > 50.0 166 (5.26) 37.0 > 50.0

159 (5.31) 37.0 > 50.0 167 (5.32) 37.0 50.0
160 (5.39) 37.0 50.0 168 (5.44) 37.0 > 50.0
161(5.45) 37.0 > 50.0 5 37.5 100.0
162 (5.29) 37.0 > 50.0 93 40.0 > 50.0
94 40.0 80.0 88 > 50.0 > 50.0
3 > 50.0 > 50.0 7 50.0 100.0
90 50.0 > 50.0 91 50.0 80.0
95 > 50.0 > 50.0 11 > 50.0 > 50.0
12 50.0 > 50.0 96 50.0 > 50.0
97 > 50.0 > 50.0 98 50.0 > 50.0
121 50.0 > 50.0 126 50.0 > 50.0
163 (5.27) 50.0 > 50.0 42 50.0 > 50.0
154 (5.28) > 50.0 > 50.0 169 (5.33) > 50.0 > 50.0
46 50.0 > 50.0 80 > 50.0 > 50.0
77 > 50.0 > 50.0 76 > 50.0 > 50.0
81 ~ > 50.0 > 50.0 173 (5.35) > 50.0 > 50.0

TABLE 16 - continued

#
Example Tumor Normal
IC50 IC50 ICso ICso
M) (M) (M) (M
170 (5.37) 50.0 > 50.0 174 (5.38) 50.0 50.0
171 (5.40) 50.0 > 50.0 87 50.0 > 50.0
172 (5.42) > 50.0 > 50.0 175 (5.43) > 50.0 > 50.0
180 (5.47) 18 > 50.0 181(5.48) < 3.1 > 50.0

In Table 16, the numbers in parenthesis in the Example column refer to the formula number for the compound used in the indicated example.

TABLE 17

Example Enzyme COS CELLS Inhibition of Tumor Cell
Inhibition Activity Growth
GGPT Inhibition of MAT Assay
IC50 (M) Ras IC50 (M)
Processing
IC50 (M) Tumor Normal
180 > 42 0.01-10 18 > 50
12.5 > 50
182 (6.4) > 40 10-100 37 > 50
183 (6.5) > 40 10-100 5 18
184 (5.60) ---- 10-100 12.5 > 50
185 5.61 ---- 10-100
187 (6.7) > 46 0.01-10 37 > 50
25 > 50
187 (6.8) > 46 0.01-10 9 > 50
4 50
189 (5.62) 42 0.01-10 37 > 50
190 (5.63) ---- ---- > 50 > 50
191 (5.64) ---- ---- < 3.1 50
192 (5.65) > 43 0.01-10 25 > 50
37 > 50

TABLE 17 - continued

Example Enzyme COS CELLS Inhibition of Tumor Cell
Inhibition Activity Growth
GGPT Inhibition of MAT Assay
IC50 (M) Ras IC50 (M)
Processing
IC50 (M) Tumor Normal
196 (5.69) > 46 0.01-10 37 > 50
25 > 50
197 (5.70) ---- 10-100 25 > 50
198 (5.71) ---- 0.01-10 12.5 > 50
200 (5.73) ---- 0.01-10 18 > 50
201 (5.74) ---- 0.01-10 3.1 12.5
206 ---- 0.01-10 < 3.1 16
208 (5.81) ---- ---- > 50 > 50
209 (5.82) ---- ---- 25 > 50
211 (5.84) ---- 37 > 50
212 (5.85) ---- ---- 25 37
217 (5.90) ---- ---- 37 50
218 (5.91) ---- ---- 37 50
219 (5.92) ---- ---- 25 > 50
220 (5.93) ---- ---- 25 > 50
221 (5.94) ---- 6.25 > 50
222 (5.95) ---- 0,01-10 18 37
223 (5.96) ---- 10-100 25 > 50
223 (5.97) ---- 0.01-10 8 8 > 50
224 (6.11) ---- 0.01-10 37 > 50
225 (5.98) ---- ---- 12.5 50
225 (5.99) ---- 0.01-10 12.5 > 50
226 (5.100) --- ---- 25 > 50
226 (5.101) ---- 0.01-10 12.5 > 50
227 (5.102) > 41 0.01-10 4 > 50
229 (5.104) ---- ---- 37 > 50
230 (5.105) ---- 10-100 37 > 50
233 (5.108) ---- 0.01-10 18 > 50

TABLE 17 - continued

Example Enzyme COS CELLS Inhibition of Tumor Cell
Inhibition Activity Growth
GGPT Inhibition of MAT Assay
IC50 (uM) Ras IC50 (M)
Processing
IC50 (M) Tumor Normal
234 > 43 0.01-10 31 > 50
235 ---- 0.01-10 12.5 > 50
236 (5.111) > 45 0.01-10 4 > 50
237 (5.112) ---- ---- > 50 > 50
238 (5.113) ---- ---- > 50 > 50
239 (5.114) ---- 0.01-10 37 > 50
246 (5.121) > 40 0.01-10 12.5 50
< 3.1 > 50
247 (5.122) > 40 0.01-10 25 > 50
8 > 50
248 (5.124) ---- 0.01-10 18 > 50
248 (5.123) ---- 0.01-10 18 > 50
250 (5.126) ---- 0.01-10 18 > 50
251 (5.127) ---- 0.01-10
261 (6.12) ---- 0.01-10

266 (5.138) ---- 0.01-10 3.1 6.25
267 (6.17) ---- 10-100
269 (5.140) --- 0.01-10 6.25 12.5
276 (5.145) ---- 0.01-10 12.5 50
281 (5.149) ---- 0.01-10 4 > 50
283 (5.151) ---- 0.01-10 10 > 50
285 (5.153) ---- 10-100 12.5 > 50
286 (5.154) ---- 0.01-10 25 > 50
287 > 40 10-100 3.1 > 50
50 > 50
25 > 50

TABLE 17 - continued

Example Enzyme COS CELLS Inhibition of Tumor Cell
Inhibition Activity Growth
GGPT Inhibition of MAT Assay
IC50 (M) Ras IC50 (uM)
Processing
IC50 (M) Tumor Normal
288 ---- 0.01-10 8 > 50
289 > 40 10-100 12.5 > 50
18 > 50
12.5 > 50
290 > 38 ---- 12.5 > 50
6.25 > 50
8 > 50
291 > 46 0.01-10 18 > 50
292 > 44 0.01-10 6.25 > 50
293 > 40 10-100 12.5 > 50
12.5 > 50
12.5 > 50
294 ---- 0.01-10 18 > 50
295 ---- 10-100
297 41 ---- > 50 > 50
298 > 35 10-100 > 50 > 50
299 1000 ---
300 ---- 0.01-10 < 3.1 > 50
301 40 0.01-10 12.5 > 50
< 3.1 > 50
< 3.1 > 50
303 > 43 0.01-10 8 > 50
304 > 40 ---- 50 > 50
305 ---- ---- 25 > 50
307 ---- 0.01-10 12.5 50
309 35.1 10-100 ---
310 ---- ---- 25 > 50

TABLE 17 continued

Example Enzyme COS CELLS Inhibition of Tumor Cell
Inhibition Activity Growth
GGPT Inhibition of MAT Assay
IC50 (IIM) Ras IC50 (uM)
Processing
IC50 (M) Tumor Normal
311 41.3 0.01-10 10 > 50

312 > 46 0.01-10 12.5 > 50
313 > 46 0.01-10 6.25 > 50
314 > 46 0.01-10 4 > 50
316 > 43 10-100 25 > 50
318 ---- ---- 37 37
321 ---- ---- 6.25 > 50
322 ---- 0.01-10 8 > 50
351 1000 0.01 -10
354 1000 ---
365 ---- 0.01-10 6.25 > 50
366 ---- 0.01-10 3.1 > 50
367 ---- 0.01-10 6.25 > 50

RESULTS:
1. Enzvmolooy:
The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC50 < 10 I1M) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

<#s> The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. Generally, the compounds of the invention are inactive or weakly active as geranylgeranyl transferase inhibitors at 20 ug/mL. For example, with reference to Table 14, the compound of Example 1 inhibits GGPT 24% at 46 uM and is at least 184fold selective for FPT inhibition. The compound of Example 2, for example, inhibits GGPT 25% at 46 pM and is at least 98-fold selective for
FPT inhibition. For another example, the compound of Example 3 inhibits
GPPT 3% at 39 pM and is at least 59-fold selective for FPT. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Rastransformed cells.

2. Cell-Based: COS Cell Assay
Western blot analysis of the Ras protein expressed in Ras-transfected
COS cells following treatment with the tricyclic farnesyl protein transferase inhibitors of this invention indicated that they inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras (see Table 15).

The compound of Example 1, for example, inhibited Ras-CVLS processing with an IC50 value of 0.01-10 pM, but did not block the geranylgeranylation of Ras-CVLL at concentrations up to 20 llg/mL.

Microscopic and photographic examination of the Ras-transfected COS cells following treatment with two of the tricyclic farnesyl transferase inhibitors of this invention indicated that they also blocked phenotypic changes induced by expression of oncogenic Ras. Cells expressing oncogenicRas-CVLS or Ras-CVLL overgrew the monolayer and formed dense foci of cells. The compound of Example 1 inhibited the morphological changes induced by Ras-CVLS in a dose-dependent manner over the concentration range of 2 to 20 pg/mL. The compound of
Example 1 had little effect at 0.2 or 0.5 pg/mL. Importantly, 20 pg/mL of the compound of Example 1 did not prevent the morphological changes induced by Ras-CVLL.

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

3. Cell-Based: Cell Mat Assay
Tricyclic farnesyl protein transferase inhibitors of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

In Vivo Anti-Tumor Studies:
Tumor cells (5 x 105 to 8 x 106 of M27 (mouse Lewis lung carcinoma), A431 (human epidermal carcinoma) or SW620 (human colon adenocarcinoma [lymph node metastasis])) are innoculated

subcutaneously into the flank of 5-6 week old athymic nu/nu female mice.

For the C-f-1 (mouse fibroblast transformed with c-fos oncogene) tumor model, 2 mm3 tumor fragments are transplanted subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. Tumor bearing animals are selected and randomized when the tumors are established. Animals are treated with vehicle (beta cyclodextran for i.p. or corn oil for p.o.) only or compounds in vehicle twice a day (BID) for 5 (1-5), 6 (1-6), or 7 (1-7) days per week for 2 (x2) or 4 (x4) weeks. The percent inhibition of tumor growth relative to vehicle controls are determined by tumor measurements. The results are reported in Table 18.

TABLE 18
In-Vivo Anti-Tumor Results

s.c. Route & EX EX EX EX EX EX EX
Tumor Schedule 2 1 3 7 78 79 75
M27 po, BID. 61.2 ------ 27.3 58.2 ------ -----
1-7, x4
A431 ip,BID, ------- 20.5 0 0
1-5, x4
A431 po, BID 45.6 ------- 8 29.1
1-5, x4
A431 po, BID, 36.5 ------ 26
1-5, x4
A431 po,BID, ------ ------ ------ ------ 31 0 34.5
1-6, x4
C-f-1 ip, BID. 8 0 8 39.7
1-5, x2
C-f-1 po, BID. 9.6 ------ 0 39.3
1-5, x4
C4-l po, BID, ------- ------- 26.7 25 20
1-5, x4
SW- ip, BID, 0 0 27 19.6
620 1-5, x4
SW- po, BID, 46.1 0 15.8 48.6
620 1-5, x2

TABLE 18 - continued

s.c. Route & EX EX EX EX EX EX EX
Tumor Schedule 2 1 3 7 78 79 75
SW- po, BIC. 33.5 ------ ------ 0
620 1-5, x4
SW- po, BID, ------- ------- 59.6 26.7 43.4
620 1-5, x4

Additional in-vivo anti-tumor results are reported in Table 19. In
Table 23, LOX is a human memanoma cell line, and the schedule "10/wk, x4", for example, means 10 times per week (twice a day Monday to Friday) for 4 weeks.

TABLE 19
In-Vivo Anti-Tumor Results

Example Tumor Dose Route & Average
or (MPK) Schedule % Tumor
Structure Inhibition
Ex. 2 SW620 100 ip, 10/wk, x2 0

SW620 100 po, 10/wk, x2 0
SW620 100 po, 10/wk, x4 1
M27 100 po, 14/wk, x4 45
Ex. 4 SW620 100 po, 10/wk, x4 2
Ex. 7 SW620 100 po, 10/wk, x2 13
SW620 100 po, 10/wk, x4 0
M27 100 po,14/wk,x4 40
Ex. 45 SW 620 100 po, 1 0/wk, x4 0
SW620 100 po, 10/wk, x4 19
M27 100 po, 10/wk, x3 0
Ex. 47 SW620 100 po, 10/wk, x4 0
SW620 100 po, 10/wk, x4 30
M27 100 po, 10/wk, x3 19
Ex. 49 SW620 100 po,10/wk, x4 0
SW620 100 po, 10/wk, x4 27
M27 100 po, 10/wk, x3 30

TABLE 19 - continued

Example Tumor Dose Route & Average
or (MPK) Schedule % Tumor
Structure Inhibition
Ex. 75 SW620 100 po, 10/wk, x4 26
SW620 100 po, 10/wk, x4 4
SW620 100 po, 10/wk, x4 54
SW620 100 po, 10/wk, x4 7
M27 100 po,10/wk,x4 0
Ex. 82 SW620 100 po, 10/wk, x4 25
SW620 100 po, 10/wk, x4 32
Ex. 88 SW620 100 po, 1 0/wk, x4 43.25*
M27 100 po, 10/wk, x4 19
SW620 100 po, 10/wk, x4 38*
LOX 100 po, 10/wk, x4 70
SW620 100 po, 10/wk, x4 38
SW620 100 po, 10/wk, x4 37
SW620 50 po, 10/wk, x4 30
SW620 50 po, 10/wk, x4 30
SW620 25 po, 10/wk, x4 4
SW620 25 po, 10/wk, x4 0
SW620 100 po, 10/wk, x4 27.4*
LOX 100 po, 10/wk, x4 33
SW620 100 po, 10/wk, x4 28
SW620 100 po, 10/wk, x4 38
Ex. 127 SW620 100 po, 10/wk, x4 25
SW620 100 po, 10/wk, x4 42
M27 100 po, 10/wk, x3 22
Ex. 187 (6.8) SW620 100 po, 10/wk, x4 11
SW620 100 po, 10/wk, x4 21
Ex. 192 SW620 100 po, 10/wk, x4 29
SW620 100 po, 10/wk, x4 40
Ex. 287 SW620 100 po, 10/wk, x4 14
SW620 100 po, 10/wk, x4 0
Ex. 290 SW620 100 po, 10/wk, x4 41
SW620 100 po, 10/wk, x4 16

TABLE 19 - continued

Example Tumor Dose Route & Average
or (MPK) Schedule % Tumor
Structure Inhibition
Ex. 293 SW620 100 po, 10/wk, x4 5
SW620 100 po, 10/wk, x4 47
Ex. 301 SW620 100 po,10/wk,x4 16
SW620 100 po, 10/wk, x4 0
Ex. 82A SW620 100 po, 10/wk, x4 27
SW620 100 po, 10/wk, x4 26
Ex. 342 SW620 100 po,10/wk,x4 39
SW620 100 po, 10/wk, x4 31
5.21 SW620 100 po, 10/wk, x4 19
SW620 100 po, 1 0/wk, x4 17
M27 100 po,10/wk,x4 0
5.25 SW620 100 po,10/wk,x4 7
SW620 100 po, 10/wk, x4 36

Average of several results
The compound of Example 342 (Table 19) is:

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g.

magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form.

In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements. of the patient and the

severity of the condition being treated.

Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples
EXAMPLE A
Tablets

No. Ingredients mg/tablet mg/tablet
1. Active compound 100 500
2. Lactose USP 122 113
3. Corn Starch, Food Grade, 30 40
as a 10% paste in
Purified Water
4. Corn Starch, Food Grade 45 40
5. Magnesium Stearate 3 7
Total 300 700

Method of Manufacture
Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes.

Granuiate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules.

Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B
Capsules

No. Ingredient mg/capsule mg/capsule
1. Active compound 100 150
2. Lactose USP 106 123
3. Corn Starch, Food Grade 40 70
4. Magnesium Stearate NF 7 7
Total 253 1 700

Method of Manufacture
Mix Item Nos. 1,2 and 3 in a suitable blender for 10-15 minutes.

Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable twopiece hard gelatin capsules on a

suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art.

All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS
1. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Formula 1.0:

or a pharmaceutically acceptable salt or solvate thereof, wherein:
one of a, b, c and d represents N or NR9 wherein R9 is O", -CH3 or -(CH2)nCO2H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR1 or CR2; or
each of a, b, c, and d are independently selected from CR1 or CR2;
each R1 and each R2 is independently selected from H, halo, -CF3, -OR10, -COR10, -SR10, -S(O)tR11 (wherein t is 0,1 or 2), -N(R10)2, -NO2, -OC(O)R10, -CO2R10, -OCO2R, -CN, -NR10COOR, -SRC(O) OR, -SR11N(R75)2 (wherein each R75 is independently selected from H and -C(O)OR11), benzotriazol- 1 -yloxy, tetrazol-5-ylth io, or substituted tetrazol5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR10 or -C02R10; ;
R3 and R4 are the same or different and each independently represents H, any of the substituents of R1 and R2, or R3 and R4 taken together represent a saturated or unsaturated C5-C7 fused ring to the benzene ring;
R5, R6, R7 and R8 each independently represents H, -CF3, -COR10, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR10, -SR10, -S(O)1R, -NR10COOR, -N(R10)2, -NO2, -COOR10, -OCOR10, -OCO2R11, -CO2R10, OPO3R10 or one of R5, R6, R7 and R8 can be taken